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16. ABSTRACT

This report on metal toxicology contains reviews on twenty-three metals. These have been written for inclusion in a Handbook on the Toxicology of Metals: Environmental and Occupational Aspects which is being prepared by the Scientific Committee on the Toxicology of Metals of the Permanent Commission and International Association of Occupational Health. The metals covered in this volume are: aluminum, antimony, arsenic, barium, beryllium, bismuth, cadmium, chromium, cobalt, copper, germanium, indium, lead, mercury, molybdenum, silver, tellurium, thallium, tin, titanium, tungsten, uranium, and zinc.

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TOXICOLOGY OF METALS - Volume II

By

Subcommittee on the Toxicology of Metals
Permanent Commission and International Association of
Occupational Health
Prof. Lars Friberg, Chairman

in cooperation with

The Swedish Environmental Protection Board, and
The Karolinska Institute

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INTRODUCTION

Introduction to Volume I:

At the time of the XVIth International Congress on Occupational Health in Tokyo in 1969 the Permanent Commission and International Association of Occupational Health decided to form a subcommittee on the toxicology of metals. The need for such a group had been recognized during an international meeting on mercury toxicology in 1968. The subcommittee was formed with Prof. Lars Friberg of Stockholm as chairman. The program developed by this group consisted of exploration and documentation of the general principles of metal toxicology by means of symposia and workshops of experts in the field. A broad approach was selected including general environmental exposures as well as those related to occupation. Emphasis was placed on greater depth and precision of understanding in terms of metabolic processes and dose-effect relationships. The Permanent Commission, the Swedish Environmental Protection Board, and the Karolinska Institute have supported the committee in carrying out this program. Two workshops were conducted, one in conjunction with the meeting of the Permanent Commission in 1971, and another in conjunction with the XVIIth International Congress on Occupation Health in 1972.

Recently the subcommittee has decided to broaden its work by preparing a handbook on metal toxicology which will contain the general material being developed in its workshops and also specific information on a large number of metals for use by toxicologists and occupational and environmental health workers. The Environmental Protection Agency is cooperating with the other sponsors in supporting this phase of the subcommittee's work. As information is developed on the subject it will be collected in three annual progress reports. The first of these is contained in this volume. It consists of the conclusions of the subcommittee's third workshop which was held in Tokyo in 1974. Since the three workshops which have been held constitute a cumulative series, with frequent reference back to previous definitions and statements, it was thought best on this occasion to reproduce all of them together as a unit.

Introduction to Volume II:

This second volume on Toxicology of Metals contains material prepared for the Handbook on the Toxicology of Metals - Environmental and Occupational Aspects which is being prepared by the Scientific Committee on the Toxicology of Metals of the Permanent Commission and International Association of Occupational Health. It is intended to have chapters on thirty metals in the completed handbook. Twenty-three of these are available at this time and make up the contents of this volume. Although these are finished chapters, it has occurred to the authors and editors that publication at this time offers the opportunity to solicit comments and suggestions from the scientific community which might be helpful in improving these texts before final publication in the handbook. Readers who know of additional pertinent material which should be included, or have other suggestions for improvements are urged to communicate directly as soon as convenient with the responsible senior authors whose addresses are given below:

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ALUMINUM

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1. Abstract

No reliable data exist on absorption of aluminum. Some absorption should occur as aluminum is found in human organs. The lungs invariably show the highest concentration. Aluminum is found in the fetus. The biological half-time is not known but there is no tendency toward an increase of aluminum concentrations in organs with age. It has been suggested that aluminum is an essential metal, but a final answer to this question can not be given at present. Pulmonary fibrosis has been described after inhalation of aluminum in certain industrial operations. Aluminum may cause hypophosphatemia by forming insoluble phosphate complexes in the gastrointestinal tract.

A review of environmental and health aspects of aluminum has been given by Sorensen et al. (1974).

2. Physical and chemical properties

Aluminum, Al, atomic weight 27.0; atomic number 13; density 2.7; melting point 660.4°C; boiling point 2467°C; crystalline form silver-white ductile metal, cubic; oxidation state 3. Some compounds of interest are aluminum oxide, aluminum sulfate, aluminum hydroxide, aluminum fluoride, aluminum chloride and aluminum-glycole complex.

Technical aluminum oxide, which is used in the industrial production of aluminum metal, consists of two main crystal modifications, α-Al_2O_3 and γ-Al_2O_3 of different toxicological importance. Aluminum forms highly reactive organic compounds, some of which become hot and fume violently when exposed to air.

3. Methods and problems of analysis

Colorimetric and fluorescence methods as well as titrimetric methods for aluminum suffer the drawback of interference from other substances present in biological materials. Separation and preconcentration of samples present definite problems as no reagent specific to aluminum exists. Emission spectroscopy is a specific and sensitive method in which preparation and manipulation of the samples are kept to a minimum. This is an important consideration since the abundance of aluminum in the environment can easily lead to contamination of samples. A detection limit of 1 to 0.1 µg has been reported (Lander et al., 1971).

Atomic absorption seems today to be the method favored for routine analytical determination of aluminum in biological materials. A reported detection limit of 1 mg/l can be improved to 0.01 mg/l with benzene extraction (Hsu and Pipes, 1972). Using flameless atomic absorption, a detection limit of about 0.03 ng with a coefficient of variation of about 5 % has been obtained (Fuchs et al., 1974).

Neutron activation, polarography and X-ray fluorescence have been used for aluminum analysis, but these methods do not seem to possess special advantages. Even if neutron activation seems to offer the best detection limit, other methods are sufficient for most toxicological work.

A review of analytical methods for the determination of aluminum has been given by Sorensen et al. (1974), but no comparison of the different methods has been published.

4. Production and uses

4.1 Production

Aluminum is the most common metal in the earth's crust (8.13 %). Aluminum is not found in an uncombined state in nature, but mostly in the form of various silicates. Important aluminum-containing silicates are bauxite and cryolite. The raw material for the aluminum oxide is usually bauxite, the oxide being produced by sedimentation of aluminum hydroxide after caustic treatment of the raw material, followed by calcination. Aluminum metal is produced by the electrolysis of aluminum oxide in smelted cryolite at a temperature of about 970°C. Aluminum fluoride and calcium fluoride are added to the bath in addition to the fluoride-containing cryolite. The main component of technical aluminum oxide is α-Al_2O_3; the amount of γ-Al_2O_3 depends on the calcinating temperature used. The γ-modification is converted to the α-modification at temperatures higher than 900°C. The world production of aluminum has increased from 602 thousand tons in 1938 to about 14 million tons in 1974 (Baudart, 1975).

4.2 Uses

Aluminum has a variety of industrial uses, the most important being electrical engineering, household utensils and appliances, the transport and building industry, and as packaging material. About one third of the world production of aluminum is now (1973) used in the transport industry, and about half that amount in electrical engineering. The building industry in various industrialized countries utilizes from 10 to 20 % of the world production; from 10 to 15 % is utilized in packaging (Baudart, 1975). Aluminum compounds are utilized in the processing, packaging and preservation of food and as food additives for various purposes. Aluminum sulfate is widely utilized for sedimenting particles in the treatment of drinking water. Aluminum and aluminum compounds are used therapeutically to prevent hyperphosphatemia in renal disease, and in the prevention of silicosis. Other therapeutic uses of aluminum compounds are as an antacide, as an antidote, as an antiperspirant and as an adjuvant for vaccines, toxoids and for aluminum penicilline.

5. Environmental levels and exposures

5.1 General environment

5.1.1 Food and daily intake

Most unprocessed food items contain less than 10 mg Al/kg. Use of aluminum in the processing and storing of food increases the aluminum content, but not to a toxicologically significant extent. Some vegetables and fruits may contain up to about 150 mg Al/kg. The daily intake of aluminum from food may thus show a considerable variation dependent on the diet (Schlettwein-Gsell and Mommsen-Straub, 1973; Sorensen et al., 1974). Total daily intake of aluminum may amount to about 80 mg/day, as reviewed by Sorensen et al. (1974).

5.1.2 Water, soil and ambient air

Aluminum in ocean water generally is reported up to about 1 mg/l, this value being one-tenth of the concentration reported in rivers and lakes. The activities of man increase the aluminum content in surface water, but aluminum is generally not regarded as a water pollution problem. Concentrations of aluminum as high as 150-600 g/kg have been reported in soil. Aluminum content in urban air is reported up to about $10\ \mu g/m^3$; in non-urban areas values lower than $0.5\ \mu g/m^3$ are usually reported (Sorensen et al., 1974).

5.2 Working environment

Occupational exposure to aluminum and aluminum compounds is widespread, but the exposure has only to a limited degree turned out to be of toxicological importance. Exposure to aluminum oxide-containing dust in the production of abrasives from bauxite has been described as a hazard (Shaver and Ridell, 1947), but exposure levels have not been reported.

6. Metabolism

6.1 Absorption

The presence of aluminum in human organs indicates some absorption of ingested aluminum. Different opinions exist as to the degree of absorption.

Ondreicka et al. (1966) found no increase in the urinary excretion of aluminum or in aluminum deposition in the organs of rats when twice the normal aluminum concentration was given as chloride or sulfate in food. When the concentration was increased to about 15 times the normal, both urinary excretion and organ deposition were enhanced.

In man absorption from the gastrointestinal tract has been discussed in relation to the use of aluminum hydroxide for the treatment of hyperphosphatemia in renal failure. About 15 % absorption was found in uremic patients, with a considerable variation among individuals (Clarkson et al., 1972). Other investigators assume a much lower absorption in uremic patients (Berlyne et al., 1970; Thurston et al., 1972). Estimates of absorption of aluminum compounds other than the hydroxide or with normal kidney function have not been published. Homeostatic regulation of aluminum absorption has been suggested (Sorensen et al., 1974).

There are no data for aluminum absorption from the respiratory tract.

6.2 Distribution

Aluminum has been demonstrated in all human organs analysed, but the lungs invariably show the highest concentration, about 200 to 300 g/kg.Most other organs are reported to contain one-tenth or less of the aluminum concentration of lung tissue. Aluminum in the lung is probably a result of local deposition from inhaled air.

Increased concentrations of aluminum in food did not increase aluminum in the lungs of rats. There was a prominent increase in the liver, brain, testes and blood (Ondreicka et al., 1966). After parenteral administration to rats, increased concentrations of aluminum were found in all organs analysed, with the highest concentration in the brain (Berlyne et al., 1972).

The fetus contains aluminum, but there is no indication that the body burden of aluminum increases with age. Various diseases influence the aluminum concentration of organs (Sorensen et al., 1974).

6.3 Excretion

Parenteral administration of aluminum to experimental animals increases urinary excretion of aluminum. After peroral administration increased urinary excretion is found infrequently, probably due to a limited absorption.

In patients with renal failure, Berlyne et al. (1970) observed aluminum clearance of from 0.11 to 0.42 ml/min. These values correspond to about 5 % of the urea clearance and to 10 % of the creatinine clearance in these patients.

Aluminum in feces probably reflects the amount ingested. Ligating the bile duct in experimental animals increases urinary excretion of aluminum, indicating that biliary excretion may be of importance in gastrointestinal excretion (Soroka, 1966). Increased concentration of aluminum in bile after peroral or parenteral administration of aluminum salts has not been conclusively demonstrated.

Aluminum is a normal constituent of cow and human milk; values in the range of 1-2 mg/l are given (Schlettwein-Gsell and Mommsen-Straub, 1973).

7. Normal levels in tissues and biological fluids

Normal values of aluminum in whole blood determined by emission spectroscopy have been reported from 0.14-0.24 mg/l, plasma values from 0.13-0.16 mg/l (Sorensen et al., 1974). Berlyne et al. (1970) reported 1.46 mg/l and 0.24 mg/l as normal values in serum using neutron activation and atomic absorption, respectively. Fuchs et al. (1974), using a flameless atomic absorption technique, reported 0.037 mg/l as a normal value in serum. Tipton et al. (1966) in a balance study found less than 1 mg/l in the urine. Kehoe et al. (1940) reported a low value of 0.05 mg/l. These low values are in accordance with the assumed limited absorption of aluminum.

8. Effects and dose-response relationships

The biological role of aluminum has not been clearly established, and a definitive answer to the question of essentiality cannot be given. Failure to produce a diet free of aluminum has hampered the tests to date. A disease state caused by lack of aluminum has not been described.

8.1 Local effects and dose-response relationships

8.1.1 Animals

By intratracheal instillation both salts of aluminum and metallic aluminum powder have been found to produce pulmonary fibroses (Stacy et al., 1959; Corrin, 1963). Aluminum silicate minerals cause a limited fibrous reaction. The γ-oxides seem to produce the fibrous reaction to a greater extent than the α-oxide.

In a recent paper Gross et al. (1973) could not demonstrate fibrosis following inhalation of metallic aluminum powders in hamsters, guinea pigs or rats, but fibrosis was demonstrated after intratracheal injections of high doses. No such reaction was found with lower doses. They assume that fibrosis after intratracheal injection is caused by the injection procedure combined with high doses of dust. Pulmonary proteinosis was, however, demonstrated with both inhalation and intratracheal injection. Acute pulmonary reactions have been demonstrated with a number of aluminum compounds, among which were also more complex aluminum compounds, such as a glycole complex used as an antiperspirant (Drew et al., 1974).

Intraperitoneally injected, aluminum compounds generate fibrotic peritonitis.

8.1.2 Humans

A fibrotic lung disease in workers exposed to fine powdered aluminum metal has been clearly documented, but the mean exposure level recorded for time periods of 30 to 90 minutes per shift was 95 mg/m^3 respirable dust. Severe and sometimes fatal lung damage has been reported in workers exposed to 10-50 mg/m^3 respirable dust of aluminum metal in the production of explosives and fireworks (Mitchell et al., 1961). Human pulmonary fibrotic reaction caused specifically by other aluminum-containing dusts such as aluminum oxide has yet to be documented properly. The condition reported by Shaver and Ridell (1947) was probably a result of a combined exposure to aluminum oxide and silica, and the disease reported by Kubic (1960) may have been caused by accompanying chromate exposure. When used for the prevention of silicosis, aluminum itself has given rise to fibrosis.

8.2 Systemic effects and dose-response relationships

8.2.1 Animals

A picture of severe aluminum intoxication characterised by lethargia, anorexia and death has been described after parenteral and oral administration of aluminum hydroxide, chloride and sulfate to rats (Berlyne et al., 1972). These results have been disputed by others who claim aluminum hydroxide to be relatively non-toxic, and the toxic symptoms to be related to phosphate depletion (Thurston et al., 1972). Experimental animals fed 100 to 200 mg/kg aluminum chloride in long term experiments show retardation of growth and disturbances of phosphate and carbohydrate metabolism (Sorensen et al., 1974). Some aluminum compounds have been studied as food additives. In small amounts (1% - 2%) they stimulated growth, but it was reported that higher amounts gave rise to retardation of growth with grave disturbances of phosphate and calcium metabolism (Sorensen et al., 1974).

8.2.2 Humans

Excessive occupational exposure leads to increased aluminum uptake with recorded changes in some serum enzymes, the relevance of which to health is uncertain. Most experience with the toxicity of aluminum in man comes from the use of aluminum hydroxide in the prevention of phosphate retention in uremic patients. It must be assumed that the administration of aluminum to these patients leads to an increased absorption.

To what extent the kidney damage causes increased retention is uncertain. On the basis of an increased retention of aluminum in uremic patients maintained on aluminum hydroxide treatment, Alfrey et al. (1976) suggested that the dialysis encephalopathy syndrome is caused by an aluminum intoxication.

Otherwise, no systemic effects except those caused by hypophosphatemia have been described in such patients. Hypophosphatemia may also be induced by using aluminum hydroxide as an antacide.

8.3 Carcinogenic effects

Carcinogenicity studies have failed to produce cancer in experimental animals.

8.4 Interaction with phosphorus metabolism; aluminum and fluorides

Aluminum compounds form insoluble salts with phosphorus in the gastrointestinal tract and large amounts given perorally may thus induce a phosphorus depletion syndrome with depletion of red cell ATP. Other changes in phosphorus metabolism with unknown mechanisms which may not be related to the complex formation have also been reported (Sorensen et al., 1974).

The main health hazard in primary aluminum production is fluoride exposure, not exposure to aluminum or aluminum oxide. Both gaseous and particulate fluorides are found in the working atmosphere as well as in the emissions. Exposure levels of up to 20 mg/m^3 of total dust have been reported in modern plants; fluoride levels were mostly below 2.5 mg/m^3 (Gylseth and Jahr, 1975).

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ANTIMONY

Carl-Gustav Elinder and Lars Friberg

1. Abstract

Antimony has two valences, 3 and 5. Most absorbed antimony is excreted rapidly via urine and feces. Elimination and route of excretion are dependent on the type of antimony compound. The urinary excretion seems to be higher for pentavalent than for trivalent antimony compounds. Gastrointestinal excretion is higher for trivalent than for pentavalent antimony. Some data on humans indicate that a small part of absorbed antimony may have a long biological half-time. After acute or chronic exposure to antimony the highest concentrations will be found in thyroid, adrenals, liver, and kidney.

Industrial exposure may give rise to irritative symptoms from the respiratory tract. After long-term exposure, pneumoconiosis, sometimes with obstructive lung diseases, has been observed. Heart effects, even fatal, have been observed as a result of long-term industrial exposure to antimony trioxide, and as side effects in connection with treatment of parasitic diseases with antimony compounds. Cardiovascular effects have been observed also in animal experiments.

The primary route of exposure for normal people is usually via food.

2. Physical and chemical properties

Antimony, Sb, atomic weight 121.8; atomic number 51; density 6.7; melting point 631°C; boiling point 1750°C; crystalline form silver-white metal, hexagonal; oxidation state 3, 5. Compounds to be mentioned in this chapter are antimony trioxide, antimony trisulfide, antimony trichloride, antimony pentasulfide, antimony potassium tartrate, antimony pentoxide, stibine, sodium antimony dimercaptosuccinate.

Antimony belongs to the same periodic group as arsenic, which it resembles both chemically and biologically. It exists in both organic and inorganic complexes. Stibine is an odorless, highly toxic gas.

3. Methods and problems of analysis

Antimony in air and biological materials has been determined polarographically, spectrographically and colorimetrically using Rhodamine B (Tabor et al., 1976). Neutron activation and atomic absorption spectrophotometry are now the chief methods used. Kennedy et al. (1962) reported a detection limit of 1.0 µg/kg lung tissue employing neutron activation and Dams et al. (1976) using the same principles could detect 1 ng Sb/m^3 air. AAS had a detection limit around 0.5 mg Sb/l in a water solution (Christian and Feldman, 1970). Recently a hydride generation technique with subsequent atomic fluorescence determination was reported to have a detection limit of 0.1 µg Sb/l in concentrated hydrochloric acid (Thompson, 1975).

Precision and accuracy of the methods for different materials have not been studied.

A colorimetric method used for determination of stibine (SbH_3) in air had a detection limit of 50 µg Sb/m^3 (Short and Wheatley, 1962).

4. Production and uses

4.1 Production

In nature antimony occurs in association with sulfur, forming stibnite. Other minerals containing antimony are cervanite, valentinite and kermesite.

The world production of antimony, which has generally increased at a rate of about 3 % per annum, was 69,400 metric tons in 1973. The leading producers were South Africa with 15,483 tons, Bolivia with 14,719 tons and the People's Republic of China with 12,000 tons.

4.2 Uses

Antimony is a common constituent of alloys with other metals, such as lead and copper. Antimony compounds are used for producing fireproofing chemicals and textiles.

In the USA antimonial lead accounts for 38 %, fireproofing chemicals and compounds for 14 % and ceramics and glassware for 11 % of the industrial consumption. Other important industrial uses are in bearing metals and pigments (Wyche, 1972).

Some antimony compounds, particularly tartar emetic, are used against parasitic diseases and infections (Goodman and Gilman, 1941; Liu et al., 1958; Ciplea et al., 1966; Arfaa et al., 1967; Pedrique et al., 1970).

5. Environmental levels and exposures

5.1 General environment

5.1.1 Food and daily intake

Data on daily intake are controversial. Reports range from about 10 µg in a Swedish balance study using neutron activation on four subjects (Wester, 1974) to 250-1250 µg in a USA study on institutional diets for children, using atomic absorption spectrophotometry without extraction (Murthy et al., 1971). In fresh water fish antimony concentrations have been reported to be in the order of 3 µg/kg wet weight (Uthe and Bligh, 1971)

5.1.2 Water, soil and ambient air

In the Rhine River, antimony averages 0.1 µg/l; 0.2 µg/l has been reported from the northeastern Pacific Ocean (Schmidt, 1968; Spencer et al., 1970).

In soil antimony usually ranges from 0.1 to 10 mg/kg dry weight (Bowen, 1961; Khatamov et al., 1967).

Brar et al. (1970) and Dams et al. (1970) using neutron activation reported concentrations of antimony in Chicago air ranging from 1.4 to 55 ng/m^3 and an average of 32 ng/m^3, respectively.

5.1.3 Cigarettes

Antimony in cigarettes has been studied by means of neutron activation by Nadkarni and Ehman (1970). The tobacco, on the average, contained 3.1 mg Sb/kg dry weight. The amount of inhaled antimony was estimated to 20 %.

5.2 Working environment

Air concentrations of antimony in the order of 1 to 10 Sb mg/m^3 have been reported from different smelter operations. Renes (1953) found average working zone concentrations of antimony ranging from 4.7 to 10.2 mg/m^3 in smelting works. In an abrasives plant studied by Brieger et al. (1954), the average air concentration was 3.0 mg/m^3.

Stibine (SbH_3) was found to have evolved during charging of lead storage batteries in which antimony was a compound of the negative grid (Haring and Compton, 1935).

6. Metabolism

Antimony is considered a non-essential metal.

6.1 Absorption

6.1.1 Inhalation

Data on respiratory absorption of antimony are lacking.

6.1.2 Ingestion

About 15 % of a single oral dose of labelled antimony potassium tartrate to mice is absorbed, i.e. recovered in urine and tissues (Waitz et al., 1965). The absorption might, however, be higher since simultaneous gastrointestinal excretion takes place. Thus, Gellhorn et al. (1946), following intraperitoneal administration of antimony potassium tartrate to hamsters, observed a fecal excretion of 50 % of the given dose (0.43 mg)in 24 hours.

6.2 Distribution

6.2.1 Animals

Antimony given as a single dose or by repeated injections is found in kidney, liver (Boyd et al., 1931: pentavalent antimony to monkeys; Hassan, 1938: trivalent antimony to dogs and monkeys; Goodwin and Page, 1943: pentavalent antimony to mice) and thyroid (Brady et al., 1945: trivalent antimony to dogs).

In rats fed a diet containing 2 % antimony trioxide for 1 1/2 months, the highest concentrations of antimony were found in the thyroid and adrenals, with 88.9 and 67.8 mg/kg, respectively (wet or dry weight not stated). Spleen, lungs, liver, and kidneys had concentrations between 6.7 and 18.9 mg/kg (Westerich, 1953).

6.2.2 Humans

By surface body scanning of persons given intravenous injections of labelled antimony, as sodium antimony dimercaptosuccinate, liver, thyroid and heart were seen to receive the highest amounts. Forty-three days after the last injection, the liver still showed values of about 1/6 of the maximum, which had been reached one day after the last injection (Abdallah and Saif, 1962; Abdel-Wahab et al., 1974).

6.3 Excretion

With a few exceptions data exist only for antimony salts used in medicine.

6.3.1 Animals

Rate and route of excretion are dependent on the valence of the compound. Certain species differences are also seen. In general pentavalent organic antimony is mainly excreted in urine, trivalent mainly in feces (Otto and Maren, 1950).

Six hours after intravenous and intraperitoneal injections of pentavalent antimony compounds to mice about 50 to 60 % will be found in urine. The initial excretion rate is less rapid for the trivalent form, but after 48 hours the differences between the forms decline; total urinary excretion in 48 hours is around 70 % (Goodwin and Page, 1943).

Twenty-four hours after intraperitoneal administration of tri- and pentavalent antimony to hamsters about 50 % of the trivalent and less than 10 % of the pentavalent antimony were found in feces. Corresponding excretion in urine was about 15 % and 70 % respectively (Gellhorn et al., 1946).

6.3.2 Humans

Single intravenous or intramuscular injections to volunteers produced higher 24-hour urinary excretion of pentavalent (80 %) than of trivalent (25 %) antimony compounds, a pattern similar to the one found in animals (Boyd and Roy, 1929; Goodwin and Page, 1943; Abdallah and Saif, 1962).

Out of a single intravenous dose of labelled antimony potassium tartrate (trivalent) about 80 % of excretion will take place via urine and 20 % via feces (Bartter et al., 1947). In one patient studied 73 % of the total single dose was eliminated in four weeks.

In workers exposed to air containing around 3 mg Sb/m^3, a colorimetric method showed urinary values ranging from 0.8 to 9.6 mg (Brieger et al., 1954), thus highly elevated compared to normals; see section 7.

6.4 Biological half-time

6.4.1 Animals

6.4.1.1 Inhalation

A study on beagles exposed to labelled antimony aerosols indicates an initial fast clearance, a few days, of up to 80 % of the initially deposited material (whole-body measurements). This fast excretion phase was followed by a slow clearance with a half-time in whole-body on the order of 36 to 100 days (Felicetti et al., 1974). The retention in lung in percent of initial lung burden after 4 months ranged from 0.0 to 6 % depending on type of particles. Excretion of antimony took place via urine and feces, with a ratio of 0.8. The particles had been nebulized from an antimony potassium tartrate solution passing through a heating column at 100, 500 and 1,000°C which yielded particles with aerodynamic diameters of 0.3, 1.0 and 1.3 mm.

6.4.1.3 Parenteral administration

Some animal data indicate an initial rapid clearance of antimony, involving gastrointestinal and urinary excretion. Twenty-four hours subsequent to an intraperitoneal injection given to hamsters, Gellhorn et al. (1946) found about 65 % of trivalent and pentavalent antimony compounds in feces and urine combined.

6.4.2 Humans

The initial excretion of antimony in humans is fast (see section 6.3.2). There might be a long-term component according to a study by Mansour et al. (1967). They studied antimony in blood and urine (neutron activation) in patients who, one year earlier, had been treated with antimony for bilharzia. They found averages of 6.7 µg/l and 27.6 µg/l in three persons' blood and urine respectively. Three untreated subjects had 3.4 µg/l and 6.2 µg/l in blood and urine.

7. Normal levels in tissues and biological fluids

The highest antimony concentration, around 0.5 mg/kg dry weight (about 0.1 mg/kg wet weight), is found in the lung. Liver and kidney contain about one third of the lung concentration (Kennedy, 1966; Nixon, 1967; Shic[illegible] et al., 1972, all employing neutron activation). Recently, based on Japanese autopsies, it has been reported that skin and adrenals contain slightly higher concentrations of antimony than lung and liver, 0.1 mg/kg and 0.07 mg/kg wet weight compared to 0.06 mg/kg and 0.02 mg/kg. The total body burden of antimony in an average Japanese was estimated to be about 1 mg (Sumino et al., 1975, employing the rhodamine B method).

Blood and serum concentrations of antimony in normal subjects have been reported to be 3 µg/l and 0.8 µg/l respectively (Mansour et al., 1967; Wester, 1973, both employing neutron activation). The 24 hour urinary excretion in 16 subjects ranged from 0.5 to 2.6 µg (Wester, 1973).

8. Effects and dose-response relationships

8.1 Animals

In peroral exposure, acute and chronic, antimony potassium tartrate is more toxic than antimony tri- and pentoxide. In dogs and cats, acute symptoms such as vomiting and diarrhea were produced by antimony potassium tartrate in doses on the order of 10 mg/kg. Antimony tri- and pentoxide could be given to the same animals in doses above 100 mg/kg for months without toxic manifestations (Flury, 1927).

In a long-term study, rats given 5 mg/kg as antimony potassium tartrate in drinking water showed a significantly shortened survival and average length of life (about 15 %) compared with controls (Schroeder et al., 1970).

8.1.1 Local effects and dose-response relationships

After inhalation of antimony trioxide in an average concentration of 45 mg/m^3 for 33 to 609 hours, guinea pigs showed signs of interstitial pneumonitis (Dernehl et al., 1945). Rats exposed to antimony trioxide, dose not stated, for periods up to 14 months showed, in addition to pneumonitis, lipoid pneumonia, fibrous thickening of alveolar walls and focal fibrosis (Gross et al., 1951).

8.1.2 Systemic effects and dose-response relationships

8.1.2.1 Circulatory system effects

Intravenous injections of antimony produce an acute circulatory response with fall in blood pressure (Chopra, 1927; Cotten and Logan, 1966). Pathological ECG changes have been observed. In dogs injected for four days with 3 mg of antimony potassium tartrate one of the most prominent features was inversion of the T-wave (Girgis et al., 1970).

Chronic effects with parenchymatous degeneration in the myocardium were observed upon histopathological examination of hearts from rats and rabbits exposed to 3.1 and 5.6 mg/m^3 as antimony trisulfide for six weeks (Brieger et al., 1954).

8.1.2.2 Liver and kidney effects

Fatty degeneration occurred in the convoluted tubules of the kidney and the liver after a single administration of 60 mg antimony potassium tartrate solution to rabbits. The kidney changes appeared a few hours after the administration, preceding the ones in the liver (Franz, 1937; Dernehl et al., 1945).

8.2 Humans

Data on acute and chronic toxicity of antimony to be given here come essentially from industrial airborne exposure. Adverse effects from treatment of tropical diseases with antimony compounds will be discussed only to a limited extent.

Stibine, like arsine, attacks the circulatory and the central nervous systems. Acute poisoning gives rise to headache, nausea, weakness, slow breathing and weak pulse (Stokinger, 1963).

8.2.1 Local effects and dose-response relationships

8.2.1.1 Respiratory system effects

Acute respiratory exposure to antimony trichloride (73 mg/m^3) caused irritation and soreness of the upper respiratory tract in 7 workers (Taylor, 1966). Three cases, two of them fatal, of severe pulmonary edema evoked by antimony pentachloride are described by Cordasco and Stone (1973); air concentrations were not available.

Chronic effects of antimony have been studied by Renes (1953). He examined 78 workers engaged in smelting procedures, for periods exceeding two weeks. Exposure concentrations ranged from 4.7 to 11.8 mg/m^3; 20 % of the workers suffered from rhinitis, 8 % from pharyngitis, 5.5 % from pneumonitis, and 1 % from tracheitis. Soreness and nosebleeds were experienced by more than 70 %. Brieger et al. (1954) did not mention observing respiratory tract irritation in their extensive study, discussed in section 8.2.2.1, where workers were exposed to antimony trisulfide ranging from 0.6 to 5.5 mg Sb/m^3.

Several authors have remarked upon pneumoconiosis-like X-ray pictures obtained from workers with long-term occupational exposure to antimony (Karajovic, 1958; McCallum, 1963; Browne, 1968; Cooper et al., 1968; Le Gall, 1969).

Two investigators have also observed obstructive lung changes and emphysema among antimony workers (Karajovic, 1958; Klucik et al., 1962). Klucik et al. (1962) reported on workers exposed to antimony trioxide for up to 28 years (concentration and number of workers were not given). The incidence rates of pneumoconiosis and symptoms of emphysema were 21 % and 42 % respectively.McCallum et al. (1970) have developed an X-ray method for measurement of inhaled antimony trioxide. Upon examination of 113 antimony process workers, they found a significant correlation between estimated lung antimony and period of employment.

8.2.1.2 Skin effects

Pustular skin eruptions, "antimony spots", are common among persons working with antimony and antimony salts. These eruptions are transient and mainly affect skin areas exposed to heat and those where sweating occurs (Renes, 1953; McCallum, 1963; Pashova, 1964; Stevenson, 1965).

8.2.2 Systemic effects and dose-response relationships

8.2.2.1 Circulatory system effects

Brieger et al. (1954) reported hypermortality and morbidity among workers in an abrasives industry. 124 workers were exposed to air concentrations of antimony trisulfide ranging from 0.6 to 5.5 mg/m^3 for 8 to 24 months. During this period 6 workers died suddenly and two others died of chronic heart disease. Four of the deceased were under 45 years of age. ECG changes, mostly of the T-wave, were seen in 37 out of 75 examined. During the preceding 16 years, one death had occurred in this department. No control group was examined.

8.2.2.2 Gastrointestinal effects

Acute antimony poisoning manifested as vomiting, nausea and diarrhea was reported in 150 children who drank a contaminated lemon drink (about 30 mg/l) (Werrin, 1963).

Renes (1953) reported abdominal cramps, diarrhea and vomiting among certain workers who had heavy exposures to antimony fumes in a smelter. A higher incidence of ulcer, 6 % of 111 examined antimony workers compared to that of the total plant population, 1.5 % of 3,912 employees, was seen by Brieger et al. (1954).

6.2.3 Adverse effects during antimony treatment

Various side effects and in several studies cases of sudden death have been recorded in connection with clinical treatment with antimony (El Halawani, 1968). Nausea and vomiting are common features during such treatment (Zaki et al., 1964; Hamad, 1969; Pedrique et al., 1970). Liver effects, with rises in serum GOT and GPT at the onset of therapy, were reported by Woodruff (1969). As in animal studies, ECG changes, particularly in the T-wave, are frequently reported during long-term treatment (Mainzer and Krause, 1940; Schroeder et al., 1946; Davis, 1961; Abdalla and Badran, 1963; Sapire and Silverman, 1970). Mansour and Reese (1965) have proposed that tartur emetic is an augmenting factor in the development of schistosomal myopathy.

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ARSENIC

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1. Abstract

Absorbed arsenic is distributed to various tissues and organs but is mainly excreted in the urine and feces. It has a high affinity for sulfhydryl groups in the skin, hair, and nails. Most probably because of this affinity, arsenic seems to concentrate in these tissues.

The main source of arsenic exposure in the general population is food. According to various authors, the daily intake of arsenic in the "normal" population has been reported to be from 0.07 to 0.9 mg per person. As reported in a study from the U.S.A., the body burden of arsenic is 14-20 mg and the biological half-time is relatively short. Although arsenic has not been confirmed as an essential element for human life, there is evidence that arsenic is required for the growth of some species of animals.

A number of episodes of arsenic poisoning caused by medication or contaminated food and drinking water have been reported. Skin lesions such as dermatoses, which include eruption, pigmentation, or leukodermal hyperkeratosis, may finally lead to development of a cancerous stage known as Bowen's disease. Angiosarcoma of the liver has also been reported in cases of chronic exposure to arsenic. Hemotological changes caused by arsenic poisoning have not been well documented, although anemia has been reported in some studies.

Typical arsenic poisoning among industrial workers is characterized by the perforation of the nasal septum, skin changes, and peripheral neuritis. An excessive risk of lung cancer in the production of arsenic trioxide has been observed in many studies. Workers in copper refineries, insecticide factories,

and mines may also be subjected to a high risk of lung cancer.

Epidemiological evidence indicates a cause-effect relationship between arsenic exposure and lung cancer, skin cancer, and angiosarcoma of the liver in human beings, but animal experiments have thus far failed to substantiate this relationship.

Arsine gas is a powerful hemolytic poison.

2. Physical and chemical properties

Arsenic, As; atomic weight 74.9; atomic number 33; density 5.7; melting point 817°C; boiling point 613°C sublimes; crystalline form gray metalloid, hexagonal-rhombic; oxidation state -3,0,3,5. The inorganic compounds to be taken up specifically here are the two most common ones, arsenic trioxide and arsenic pentoxide, as well as arsenic trichloride, lead arsenate, calcium arsenate, sodium arsenate, copper aceto-arsenite and arsine. Organic compounds to be mentioned include arsanilic acid, methylarsonic acid, dimethylarsinic acid and cacodylic acid.

From the viewpoint of biology and toxicology, the compounds of arsenic are classified into three major groups (Vallee et al., 1960): (1) inorganic arsenicals, consisting of trivalent arsenicals, arsenic trioxide, arsenite salts, and pentavalent arsenate salts; (2) organic arsenals and (3) gaseous arsenic or arsine (AsH_3, hydrogen arsenite). The toxicology of this last compound will be dealt with in Section 11 of this chapter. The chemical structures of more prominent arsenicals are shown in Figure 1.

3. Methods and problems of analysis

Until a few decades ago analytical methods for arsenic, which could involve procedures such as Reinsch's method, Marsh's test, and Gutzeit's test were qualitative rather than quantitative. Because of this inadequacy, analytical conclusions based on these methods have to be carefully evaluated. The heteropoly molybdenum blue method and the silver diethyldithiocarbamate method are two fairly good quantitative colorimetric methods which have a limit of detection in the range of 1-50 mg/l in a 5 l solution (Sandell, 1959).

Introduced by Holak (1969) atomic absorption spectrophotometric measurement of generated arsine gas has the potential detection limit of 0.04 µg of arsenic. Neutron activation analysis has a detection limit of 10^{10} grams for arsenic and makes possible the accurate quantitative determination of arsenic in samples such as a single strand of hair (Smith, 1959, 1964; Liebscher and Smith, 1968). Proton-induced X-ray emission analysis (PIXEA) with a detection limit of 0.1 mg/kg has been used for the simultaneous determination of arsenic and a number of other elements in biological tissues (Walter et al., 1974; Fowler et al., 1975).

In the past few years several methods for the quantitative determination of the various valence states and chemical forms of arsenic have been reported. Pulse polarography, which has a detection limit of 0.3 µg/l for arsenic in water, is capable of distinguishing the polarographically active As^{+3} from the inactive As^{+5} (Meyers and Osteryoung, 1973). A differential capture method with a detection limit on the order of 1 ng is capable of distinguishing As^{+3}, As^{+5} methylarsonic acid, and dimethylarsinic acids (Braman and Foreback, 1973). Gas chromatography and atomic absorption spectroscopy have been used to distinguish various organoarsenicals from inorganic arsenic (Daughtrey et al., 1975; Fitchett et al., 1975). A number of methods for arsenic analysis have recently been reviewed by Braman (1977).

4. Production and uses

4.1 Production

Arsenic usually exists in nature as an oxide in the trivalent state. Arsenic is obtained principally as a by-product in the smelting of copper, lead, and gold ores. When these ores are smelted, the arsenic becomes gaseous and is caught by electrostatic precipitators as a crude dust which contains relatively large amounts of arsenic trioxide. The crude dusts are roasted and the arsenic trioxide is driven off. Arsenic trioxide is collected in a cooling chamber, or arsenic kitchen, and is prepared for shipment as a material containing approximately 97% As_2O_3, the principal impurity being Sb_2O_3 (Pinto and McGill, 1953). The world production of arsenic from 1911-1972 is shown in Table 1.

4.2 Uses

Arsenic was known as a therapeutic agent as early as 400 B.C. and has since been widely used as such. From the 19th century until about 20 years ago, Fowler's solution in the inorganic form was used for the treatment of dermatoses. The organic arsenical compounds have been used for syphilis and treponematosis.

Arsenic was one of the most common homocidal poisons during the Middle Ages. Arsenicals which have been used throughout the world as agricultural chemicals include lead arsenate, calcium arsenate, copper aceto-arsenite ("Paris Green"), sodium arsenate ("Wolman Salts") and cacodylic acid.

The currently important uses of arsenic include the production of insecticides, herbicides, fungicides, and wood preservatives. It is also used in the manufacture of glass, as a bronzing or decolorizing agent, and in fabricating opal glass and enamels. Arsenicals have been used in the manufacture of dyestuffs and chemical warfare gases and in the thylox purification of industrial gases. Elemental arsenic in concentrations of 0.3% to 0.5% is utilized as an additive in the production of several alloys in order to increase hardness and heat resistance. In the livestock industry, arsenilic acid is sometimes added to swine and poultry feed as a growth promoting agent.

5. Environmental levels and exposures

5.1 General environment

5.1.1 Food and daily intake

Some kinds of food plants contain extremely small or non-detectable amounts of arsenic, whereas others grown in the same soil contain the element in measurable amounts. The degree of arsenic uptake by plants is apparently related to the concentration of soluble arsenic in soil, chemical composition of the soil and species of plant (Walshetal, 1977). Arsenic concentrations in food in USA and Japan which had not come into contact with arsenical insecticides are shown in Table 2.

Marine organisms as well as seaweed contain roughly 10 times higher arsenic concentrations than other foods. Many species of bony fish contain 2 to 8 mg/kg, oysters 3 to 10 mg/kg, mussels 120 mg/kg, clams around 11.6 mg/kg, whale meat about 0.16 mg/kg, prawns from the coastal waters of Britain up to 174 mg/kg and shrimps from the southeastern coastal waters of the USA up to 42 mg/kg (Underwood, 1971). The arsenic content of commercial fishmeals in animal feed ranges from 2.6 to 19.1 mg/kg with a mean of 6 mg/kg. Arsenic seems to be present as a highly stable organoarsenical in marine fish (Lunde, 1975, 1977; Penrose, 1977). A comparison of the arsenic levels in fish reported in 919 with those of 1970 failed to show any significant increase (International Atomic Energy Agency, 1970).

The amounts of arsenic ingested daily via food are greatly influenced by the amount of seafood in the diet. A special diet in the USA which excluded seafood contained 0.4 mg of arsenic per person per day, while an average USA diet consisted of 0.19 mg per person per day (Schroeder and Balassa, 1966). According to another study, the daily intake of arsenic as arsenic trioxide in the same country was calculated to be 0.137 to 0.330 mg per person (Duggan and Lipscombe, 1969, cited in IARC, 1973). Other sources indicate that arsenic is present in the diet at levels from 0.05 to 0.16 mg/kg per day, corresponding to an intake of 0.15 to 0.40 mg per person per day (Sommers and Smith, 1971, cited in IARC, 1973; Schroeder and Balassa, 1966). The daily intake of total arsenic in Japan was reported to be from 0.07 to 0.17 mg per person in 1960 (Nakao, 1960), and the daily intake in Fukuoka in 1974 was measured from 0.069 to 0.365 mg per person (Ishinishi et al., 1974).

5.1.2 Water and soil

Traces of arsenic can be detected almost everywhere. In most parts of the world, the arsenic content of river water averages 0.0004 mg/l and ranges from nondetectable to 0.23 mg/l (Bowen, 1966). Sea water ordinarily contains 2-5 μg/l of arsenic (Johnson, 1972). Arsenic contents of natural water in several areas of the world have been reviewed by Ferguson and Gavis (1972). The concentrations of arsenic in surface waters of the United States were found to vary from less than detectable to 1.1 mg/l (Durum et al., 1971). Methylated species of arsenic have been measured in both fresh and salt water (Braman and Foreback, 1973; Crecelius et al., 1975).

High carbonate spring waters in California, Romania, Kamchatka in the USSR, and New Zealand have been reported to contain 0.4 to 1.3 mg/l of arsenic (Schroeder and Balassa, 1966). In Japan, hot-spring water has also been found to contain relatively high concentrations of arsenic, ranging from 0.0 to 10.3 μg/l in Beppu City, Oita Prefecture, to 1.62 μg/l in Oninuki Town, Miyagi Prefecture, in one study (Kawakami, 1967).

The mean arsenic content of crystalline rock is about 2 mg/kg, while soil usually contains from 1 to 40 mg/kg. In general, arsenic tends to remain in surface layers of soil and may render it temporarily sterile to the growth of some plants, particularly legumes. It should be noted that arsenic is contained in the phosphate rock currently used to manufacture fertilizers and detergents (Vallee et al., 1960; Bowen, 1966; Schroeder and Balassa, 1966).

5.1.3 Ambient air

Major sources of arsenic air pollution are the smelting of metals, burning of coal, and use of arsenicals as pesticides. Soils are not a significant source of air pollution. Arsenic in ambient air occurs mainly in particulate form as arsenic trioxide and metal arsenites.

The 133 stations of the U.S. National Air Sampling Network reported in 1964 that the annual average concentrations of arsenic in air ranged from nondetectable to 0.75 μg/m^3. The overall average was approximately 0.02 μg/m^3 (Sullivan, 1969). The highest value, which was a quarterly average in El Paso, Texas in 1964, was 1.40 μg/m^3. In Anaconda, Montana, which had local air pollution from a metal mine and refinery, the highest ambient air concentration was 2.5 μg/m^3 in 1961 and 1962.

Coal contains 0.08 to 16 mg/kg of arsenic. In Czechoslovakia, emissions of approximately one ton of arsenic per day were reported around the Novaky power station, which burned coal containing up to 1.53 mg/kg of arsenic. In the power station flue dust, the arsenic concentration varied from 43.0 to 111.4 mg/kg (Bencko et al., 1971; Long-Term Programme, 1973).

5.1.4 Tobacco

Arsenic in tobacco originates from insecticides, especially lead arsenite. The arsenic content of various popular brands of American cigarettes averages 12.6 μg per cigarette in 1932-33 and had increased to 42 μg per cigarette in 1950-51 (Satterlee, 1956). The concentration of arsenious oxide in cigarette smoke was reported to range from 3.3 to 10.5 mg/m^3 (Thomas and Collier, 1945). Arsenic concentrations in tobacco have been reported to have declined during the last twenty years due to decreased use of arsenical pesticides (Frost, 1967).

5.2 Working environment

Studies on the measurement of arsenic concentrations in cases of occupational exposure are rare. According to Patty (1962) the highest exposure in insecticide manufacturing is usually found in the mixing, screening, drying, bagging, and drum-filling operations. He gave concentrations of arsenic in the air ranging from 0.5 to 45 mg/m^3 during such operations. A high exposure to arsenic fumes and dusts may occur in factories which manufacture As_2O_3, in smelters of copper, lead, zinc, iron, and other ores, as well as in factories which manufacture and use herbicides. According to more recent reports from Japan, arsenic concentrations in the air of well-controlled workshops in a copper refinery were 0.07 to 0.11 mg/m^3 under normally ventilated conditions, and 0.077 to 0.194 in a nonventilated condition. Kodama et al. (1975) reported average arsenic concentrations in air of 0.01 to 0.12 mg/m^3 around a furnace in a copper smelter and 0.01 to 0.07 mg/m^3 near a furnace in a ferro-nickel smelter.

6. Metabolism

6.1 Absorption

6.1.1 Inhalation

Arsenic exposure through inhalation usually occurs in the form of arsenic oxide, particularly arsenic trioxide, and arsenate compounds. In a review on size frequency distribution of arsenic trioxide dust, more than 23% of the particles were reported to be larger than 5.5 µm (Pinto and McGill, 1953). Sieve analyses of the final product of the arsenic trioxides showed that over 98% (by weight) remained on a 325-mesh sieve. This characteristic of arsenic trioxide dust causes its deposition in nasal and mouth cavities and in the upper respiratory tract. More recent analytical data on air samples collected near a copper smelter have indicated a high concentration of arsenic in particles of less than 1 µm diameter.

There are few human data which lend themselves to an exact calculation of the absorption of inhaled arsenic. One study which does include such data is that conducted by Holland et al. (1959). Eight persons were studied, and uptakes ranged from 2.2% to 8.6% of the total arsenic that had been injected into cigarettes. Holland et al. concluded that if a cigarette contained 30 μg of arsenic trioxide in the portion smoked, the average smoker would take up 2.5 μg of arsenic trioxide in the respiratory tract per cigarette.

6.1.2 Ingestion

Absorption of arsenic through food is the most significant route of exposure for the nonindustrially exposed. Coulson et al. (1935) found that of 17.9 mg/kg arsenic (assumed to be pentavalent) in shrimp fed to rats, a minimum of 0.7% was retained in the tissue, whereas of the same concentration of arsenic trioxide 18% was retained during a three-month period. The absorption of arsenic from the gut is apparently influenced by the chemical form of the arsenical involved and dietary composition (Morgareidge, 1963; Tamura, 1972).

6.2 Transport and distribution

After absorption by the lungs or the alimentary tract, arsenic is transported via the blood to other parts of the body. Hunter et al. (1942) studied the distribution of radioactive arsenical compounds after oral and parenteral administration and found arsenic in the liver, kidney, lungs, spleen, and skin during the first 24 hours after administration. Arsenic concentration in the skin increased for several days after a single administration, while in the liver and kidneys it decreased after 24 hours. Small concentrations were found in the brain, heart, and uterus. Bone and muscle concentrations of arsenic were low, but the overall amounts of arsenic in these tissues may be high due to their mass. In conjunction with the skin, they comprise the major depots of arsenic in the body. Vallee et al. (1960) noted that small quantities of arsenic, even when the dose is low, may be detected in tissues of ectodermal origin such as the hair and nails many months after it has disappeared from the urine and feces.

Inorganic arsenic does not cross the blood-brain barrier in humans, although it may do so in some anthropoids. In man and rats, arsenic is transferred across the placenta (Vallee et al., 1960). In radioactive tracer studies on arsenic in rats, 95% to 99% of the arsenic in the whole blood was detected in erythrocytes whereas in humans, monkeys and rabbits, arsenic was more equally distributed between blood cells and plasma proteins. The form of the arsenic administered, arsenate or arsenite, played a role in this distribution (Hunter et al., 1942; Hogan and Eagle, 1944; Mealy et al., 1959). In various mammalian tissue fractions, the greater part of the injected radio-arsenic is found in the protein fractions; small amounts are present in the acid-soluble portions of the tissue, and insignificant amounts are found in lipids (Lowry et al., 1942). Nucleoproteins do not combine with arsenic more than do proteins in general. The major carriers of arsenic in the plasma of mice are alpha-1 globulins. In each organ or tissue, it is known that arsenic can chemically combine with sulfhydryl groups. It has been demonstrated that trivalent arsenical toxicity can be reversed by thiol compounds of the reduced type, e.g., glutathione and cysteine (Vallee et al., 1960).

6.3 Accumulation and biological half-time

Bencko and Symon (1970) administered arsenic trioxide by inhalation or drinking water to animals and found that arsenic accumulation was biphasic and that it did not have the character of a simple saturation curve. In the first phase, the arsenic concentration increased in all organs and tissues which were investigated, and in the second phase it decreased. They concluded that the decrease of arsenic concentrations in internal organs, for example, the liver, was probably dependent on the activation or enhancement of an arsenical excretion mechanism.

About 80% of the absorbed arsenic is retained and widely distributed in tissues, such as the liver, kidney, spleen, bone marrow, skin, and the hair and nails. The biological half-times in the blood of chickens given a single oral dose of arsanilic acid or sodium arsenate were 36 hours and 60 hours respectively (Overby and Fredrickson, 1963).

Crecelius (1975, 1977) has reported biological half-times of 10 hours for As^{+3} and 30 hours for methylated forms of arsenic in a person who drank wine containing As^{+3}.

6.4 Excretion

Arsenic is excreted mainly in urine, to some extent in the feces (Hunter et al., 1942) and through normal hair loss and skin shedding. The available evidence indicates that ingested inorganic arsenate is excreted from the body mainly in the pentavalent form but some percentage may be reduced (Lanz et al., 1950; Ginsburg and Lotspeich, 1964; Ginsburg, 1965). Trivalent arsenic appears to be primarily methylated *in vivo* to methylarsonic acid and dimethylarsinic acid (Braman and Foreback, 1973; Crecelius, 1975, 1977). Excretion of methylated arsenic following exposure to airborne arsenic has been recently reported (Smith and Crecelius, 1977).

7. Levels in tissues and biological fluids, normally and as indices of exposure, intoxication and concentrations in critical organs

Studies which quantitatively indicate the relationship between arsenic concentrations in air and critical organs such as the skin are rather limited. The critical effects in these organs usually develop following a long incubation period after the cessation of exposure. Also, arsenic concentrations in critical organs are not easily measured.

Arsenic concentration in urine has been used as an index of exposure but a number of complexities such as diet and chemical forms of excreted arsenic affect this parameter. The normal body burden of arsenic in humans in the USA was concluded to be 14-21 mg based on calculations of daily intake (Schroeder and Balassa, 1966). Arsenic concentrations in organs of healthy persons from Scotland who died in accidents ranged from 0.012 mg/kg in brain to 0.460 mg/kg in hair (Liebscher and Smith, 1968). Concentrations in persons from Japan who consumed relatively high amounts of seafood ranged from 0.020 mg/kg dry weight in the pancreas to 0.892 mg/kg in the nails (Kadowaki, 1960). The former authors used neutron activation analysis and the latter polarography. Values for all organs analysed in the two studies are shown in Table 3.

7.1 Arsenic in urine

In a study of arsenic trioxide exposure, Pinto and McGill (1953) found an average urinary arsenic concentration of 0.13 mg/l and a median of 0.10 mg/l in 147 urine samples taken from 124 workers who had not been exposed to arsenic. The average arsenic concentration in urine in 835 spot samples taken from 348 men who were exposed to arsenic in the same factory as the control group was 0.82 mg/l and the median concentration was 0.58 mg/l.

Schrenk and Schreibeis (1958) reported that the average arsenic concentration in urine among 756 people without any particular exposure to arsenic was 0.08 mg/l with a range from 0.02 to 2.0 mg/l. In other studies, the concentration of urinary arsenic in persons with no known exposure has been reported as follows: 0.003-0.150 mg/l or 12-260 µg/day (Vallee et al., 1960); and 0.138 mg/l or 12-927 µg/day as the mean in a Japanese population sample (Iwataki and Horiuchi, 1959). Schrenk and Schreibeis (1958) found that ingestion of marine shellfish caused marked elevation of total urinary arsenic concentrations in humans. Crecelius (1977) has reported that the chemical form of urinary arsenic following ingestion of shellfish is markedly different from the methylated form observed after exposure to inorganic arsenic. Dietary habits should be thoroughly examined when using urinary arsenic concentrations as an index of exposure.

7.2 Blood

In general there are technical difficulties in the measurement of arsenic concentrations in the blood. According to Liebscher and Smith (1968), the concentration of arsenic in the whole blood averages 0.147 mg/l, with a range of 0.001 to 0.92 mg/l. Vallee et al. (1960) reported that the range of the arsenic concentration in whole blood was from 0.0 to 0.37 mg/l. Heydorn (1970) reported mean arsenic concentrations in whole blood of 0.022 mg/l in Taiwanese subjects using neutron activation analysis.

7.3 Hair

Normal concentrations of arsenic in hair are as follows: Smith (1964) reported that 80% of 1,000 people had below 1 mg/kg of arsenic in the hair, with an average of 0.81 mg/kg and a median of 0.51 mg/kg. He stated that hair concentrations of arsenic above 3 mg/kg should always be suspect, those that are 2-3 mg/kg require further examination, and those that are less than 2 mg/kg should not be dismissed when arsenic poisoning or heavy exposure to arsenic is suspected. Liebscher and Smith (1968) reported 0.02 to 8.17 mg/kg as the normal range for arsenic concentrations in the hair based on 1,250 persons.

The relationship between arsenic concentrations in hair and those in ambient air have been studied by Bencko et al. (1971) and Hammer et al. (1971) who reported that the mean concentration of arsenic in hair significantly reflected the degree of arsenic air pollution in communities. Hair concentrations of arsenic were found to increase depending on the magnitude of arsenic exposure via any route of entry. However, soon after arsenic exposure ceases, the hair concentration rapidly decreases and returns to a normal level within a relatively short period. Arsenic hair concentrations among retired workers who had extensive arsenic exposure may be within a normal range in spite of the fact that some of them may have other symptoms of chronic arsenic poisoning, such as arsenomelanosis, polyneuropathy, or sequelae of the poisoning (Ishinishi et al., 1973).

Lander et al. (1965) reported that the arsenic concentration of scalp hair was below 4 mg/kg (a normal value, according to them) in 6 out of 18 persons who developed acute arsenic poisoning within 24 hours of the ingestion of arsenic. The other 12 persons showed values ranging from 5 to 700 mg/kg. The distribution of arsenic along the shaft of the hair was also examined. In 8 out of 12 persons with abnormal values the highest levels were found near the hair root, while the other 4 had the highest levels near the tip. Analysis of hair offers no reliable method of distinguishing between acute and chronic intoxication. Terada et al. (1960) described an investigation of the arsenic concentration of hair in 39 cases with chronic arsenic poisoning caused by ingestion of contaminated well water for about 10 years or more. Twenty-eight percent of the total cases had 5-10 mg/kg arsenic in the hair, 26% showed below 5 mg/kg, 13% revealed either 15-20 mg/kg or 10-15 mg/kg, and the highest concentration was 85 mg/kg. There was no correlation between arsenical toxicity and arsenic concentration in the hair. Caution must be exercised in using hair concentrations of arsenic as an index of exposure following atmospheric exposure due to absorption of particles on hair shafts.

8. Effects

Arsenic may cause both acute and chronic types of poisoning. Acute poisoning by arsenic is currently rare. Both subacute and chronic poisoning usually occur because of exposure to contaminated air or drinking water. The following review will describe symptoms and signs in human beings suffering from arsenic poisoning. It will also refer to animal data, because these data may be helpful in the interpretation of effects observed in humans both from a clinical and industrial point of view and in the establishment of dose-response relationships.

8.1 Acute effects

Irritant and vesicant arsenical compounds, such as arsenic trioxide, arsenic trichloride, and the arsenical war gases, have been known to cause severe damage to the respiratory system upon inhalation. Symptoms of respiratory irritation are cough, dyspnea, and pain in the chest, especially upon inspiration. Other symptoms include giddiness, headache, extreme general weakness, and later, nausea, vomiting, colic, diarrhea, porathesis, and pains throughout the body. In addition, acute poisoning from exposure to airborne dust is frequently accompanied by irritation of any exposed skin or mucous membrane, e.g., dermatitis, nasal mucosal irritation, laryngitis, mild bronchitis, and conjunctivitis.

Cases of suicidal, homocidal, or accidental arsenical poisoning by ingestion have been frequently reported. The last may be a result of the consumption of food and liquids contaminated by food additives containing arsenic. The most common chemical form of arsenic in such cases is usually arsenic trioxide. A fatal dose of ingested arsenic trioxide for humans has been reported to range from 70 to 180 mg. Smaller amounts may cause less severe symptoms of arsenic intoxication (Vallee et al., 1960).

8.2 Chronic effects

8.2.1 General aspects; large-scale episodes and endemics

Chronic arsenic poisoning in workers after long-term exposure via inhalation is manifested in abnormalities of the skin and mucous membranes, as well as in symptoms of the gastro-intestinal and nervous systems. In a few cases, disorders of the circulatory system and the liver have been recorded. A number of studies have also disclosed systemic poisoning caused by exposure to arsenical insecticides which were mainly in the form of lead arsenate.

An episode of chronic arsenic poisoning in people living near an arsenic trioxide refinery has been reported in Japan. Victims showed several symptoms and signs of systemic arsenic poisoning, including: skin lesions and signs and symptoms of peripheral neuropathy. Since these chronic poisoning cases were discovered a number of years after the closure of the refinery, the concentration of arsenic in the ambient air of the community at the time the factory was operating is unknown. Furthermore, many inhabitants of the area with symptoms of systemic arsenic poisoning were also working in the refinery at the time, so it is difficult to distinguish whether those inhabitants were exposed occupationally or environmentally. A high incidence of chronic respiratory diseases was also observed in the same area. It is not known whether these diseases were caused by inhalation of air with high concentrations of arsenic or of high concentrations of sulfur dioxide (SO_2), which may have also been present before closure of the refinery. According to a case control study by Kuratsune (1973), a significantly higher incidence of lung cancer was also observed among the inhabitants. However, most cases of lung cancer were related to occupational exposure, and it was not elucidated whether exposure to the community's ambient air alone could be a contributory cause.

Certain respiratory and nervous symptoms (moderate hearing impairment) have been reported in children living near the Novaky power plant in Czechoslovakia mentioned in Section 5.1.2 (Symon and Bencko, 1973). Cmarko (1963, cited by Wickstrom, 1972) stated that loss of working capacity was significantly greater in the area of the power station than in other industrial areas.

Chronic arsenic poisoning from ingestion of contaminated food, beverages, and water has been reported in many countries. A report from the United Kingdom involved 6,000 people who had ingested beer contaminated by arsenic (Kelynack et al., 1900). Reports of "regional endemic chronic arsenicism" caused by drinking water with high concentrations of arsenic in and around Cordoba, Argentina, have been published by Manyano and Tello (1955) and Bergoglio (1964) (both cited by Wickstrom, 1972). These reports describe periods dating as far back as 1913. The primary criteria for diagnosis of chronic poisoning were symmetrical palmar and plantar hyperkeratosis. Excess death from cancer was seen during the period 1949-1959. Hyperkeratotic skin lesions have also been observed in populations exposed to arsenic-contaminated drinking water in Chile (Borgono and Greiber, 1972; Borgono et al., 1977). An endemic disease, also associated with arsenic in drinking water, was discovered in Taiwan in 1963 (Yeh and How, 1963; Yeh, 1963, Tseng et al., 1968; Tseng, 1977). The major manifestation was a vascular disorder resulting in gangrene of the lower extremities, commonly called Blackfoot disease. Hyperkeratotic skin lesions were also noted among the Taiwan population in question. Blackfoot disease, in contrast, was not observed among the persons with skin lesions in Chile.

The area around the Novaky power station in Czechoslovakia also contained elevated concentrations of arsenic in drinking and surface water (Somolnokyova, 1963, cited by Wickstrom, 1972). A large scale arsenic poisoning incident occurred in Japan in infants who drank powdered milk contaminated with arsenic containing phosphates in the blending process (Hamamoto, 1955). This and similar incidents in Japan have been recently reviewed in detail (Tsuchiya, 1977).

8.2.2 Skin lesions

Skin is a common critical organ in people exposed to inorganic arsenical compounds (Buchanan, 1962; Nakamura et al., 1973). Symptoms consist of eczematoid features of varying degrees of severity, but vesicular lesions tend to predominate. These latter lesions mature into more active and severe types. In occupational exposure, the lesions in the initial stage may result from local irritation and not necessarily systemic poisoning. These lesions are frequently found in areas of the skin which contain numerous moist creases, e.g. the palm of the hand and sole of the foot. An allergic type of contact dermatitis is also fraquently seen among workers who are exposed to white arsenic (arsenic trioxide). Chronic dermal lesions may follow this type of initial reaction, depending on the concentration and duration of exposure. These dermal lesions can be a result of occupational exposure, environmental exposure via drinking water, or prolonged therapeutic administration of arsenical compounds particularly Fowler's solution. Hyperkeratosis, warts, and melanosis of the skin are the most commonly observed lesions following chronic exposure.

Melanosis of the skin is a common affliction after many years' exposure to arsenic either medicinally or occupationally. It is seen most often on the upper and lower eyelids, around the temples, and on the neck, areolae of the nipples, and in the folds of the axillae. In severe cases, arsenomelanosis is observed on the abdomen, chest, back, and scrotum, along with hyperkeratosis and warts. Chronic arsenic poisoning is also characterised by depigmentation, i.e. leukodermia, especially on the pigmented areas, commonly called "raindrop" pigmentation. These skin lesions, particularly hyperkeratosis, may be related to cancer of the skin (See Section 8.3). Another characteristic of chronic arsenic poisoning is the presence of white striae in the fingernails, first described by Mees (1919). The accumulation of arsenic in skin is probably related to the abundance of proteins containing sulfhydryl (SH) groups with which arsenic readily reacts. It should even be noted that the adverse effects on the skin may develop long after the cessation of exposure when arsenic concentrations have decreased to normal levels (Pinto and McGill, 1953; Vallee et al., 1960; Buchanan, 1962).

8.2.3 Mucous membrane lesions

In the subchronic stage, dermatitis of the face and eyelids is sometimes accompanied by conjunctivitis, characterised by redness, swelling, and pain. Keratoconjunctivitis, a severe type, was reported following exposure to calcium arsenate as an insecticide. Corneal anaesthesia accompanied by a corneal ulcer has also been reported, but this may have been a very rare case. There may be irritation of the nose and pharynx in the subchronic stage, causing acute or chronic rhinitis as well as irritation of the bronchial passages.

As a result of irritation of the upper respiratory organs by arsenic dust, perforation of the nasal septum is a common finding among workers who have been occupationally exposed. The perforation, as with similar lesions caused by other chemical irritants such as chromium, is confined to the cartilagnous portion of the septum (Kiesselbach's area) and does not lead to deformity of the nose or other apparent subjective symptoms once inflammation has subsided. Many of the people who have this perforation are unaware of its presence.

8.2.4 Gastrointestinal disturbance

Chronic arsenic intoxication by ingestion has been recognised for many years and is usually characterised by weakness, loss of appetite, gastrointestinal disturbances, and on occasion, peripheral neuritis, hepatitis, keratitis, and pigmentation. However, gastroenteritis in relation to arsenic poisoning is not a common occurrence (Buchanan, 1962).

8.2.5 Peripheral nervous disturbance

Peripheral neuritis affecting mainly the upper and lower extremities is one of the symptoms of chronic arsenical poisoning. The neuritis caused by arsenic poisoning is symmetrical, widespread, and painful, aspects which do not characterise peripheral neuritis caused by lead poisoning. In severe cases of arsenic poisoning, personality alterations may occur along with headache, drowsiness, aphasia, and disorientation. Nerve biopsies from patients with such symptoms showed neuronal degeneration thought to result from inhibition of the pyruvate oxidase complex (Vallee et al., 1960). Among patients with chronic arsenic poisoning, not only bilateral polyneuropathy but also unilateral polyneuropathy without any motor paralysis has occurred. These cases showed a diminishing sensation of touch with numbness of extremities, and a "pins and needles" sensation (parathesias). These symptoms were observed among retired workers who had been heavily exposed to arsenicals and who also revealed skin lesions or perforation of the nasal septum. Takahashi (1974) reported abnormal electromyograms (EMG) among people who had lived near an arsenic mine and smelter and who were without subjective symptoms. Typical arsenical skin lesions among these inhabitants have not been confirmed.

8.2.6 Anemia

Anemia and disturbance of the hematopoietic system are not common in chronic arsenical poisoning caused by industrial exposure but anemia has been observed in chronic arsenic poisoning caused by long-term ingestion. Cases of chronic arsenic poisoning with skin lesions are often accompanied by moderate anemia and leukopenia. This type of anemia is not considered to be due to the deficiency of iron but thought to be similar to aplastic anemia from a hematological viewpoint (Terada et al., 1960; Yoshikawa et al., 1960; Terada, 1973). Anemia caused by arsine is due to hemolysis and is quite different in nature from arsenical poisoning (See Section 11).

8.2.7 Liver disturbance

Inorganic arsenical compounds have long been considered capable of damaging the liver under certain circumstances. However, this has not occurred with any reported frequency among industrial workers. On the other hand, as a sequela of arsenical medication, jaundice sometimes accompanied by ascites has been reported. One of the first records of cirrhosis among vineyard workers who used arsenic as a pesticide was reported by Dorle and Ziegler (1930). This report mentioned that arsenic poisoning was not caused by inhalation nor by skin contact, but most probably by the ingestion of wine contaminated by arsenic. More recently, similar cirrhotic changes have been noted in livers of other vintners (Butzengeiger, 1940, 1949; Luchtrath, 1972). Similar findings have also been observed among Japanese following outbreaks of mass arsenic poisoning (Tsuchiya, 1977). In addition, liver disturbances from long-term arsenic ingestion are frequently complicated by chronic hepatitis, an enlarged tender liver, and ascites.

The cellular mechanisms of arsenic hepatotoxicity appear to involve mitochondrial damage with subsequent impairment of tissue respiration (Fowler et al., 1977; Schiller et al., 1977; Woods et al., 1977).

Finally, primary liver cancer and hepatobiliary cancer caused by arsenicals have been reported as a result of either medication or industrial exposure (See Section 8.3).

8.2.8 Disorder of the heart and circulation

The epidemiological and clinical evidence for primary cardiac injury in arsenic workers is not very definite, but electrocardiograms have revealed abnormalities (Barry and Herndon, 1962; Glazener, 1968). Abnormal electrocardiograms indicating a toxic myocardial effect were found among vineyard workers with chronic arsenical poisoning who used arsenical insecticides. These cases showed other symptoms of the poisoning as well. Some of the workers with severe myocardial injury also suffered from peripheral vascular disturbances, endo-angitis, gangrene of the extremities, atrophic acrodermatitis, and other less severe symptoms of peripheral blood vessel damage (Butzengeiger, 1940, 1949; Hadjioloff, 1940). As mentioned earlier, the Blackfoot disease in an arsenic-exposed population in Taiwan is due to peripheral vascular disorders (Yeh and How, 1963; Yeh, 1963).

8.3 Carcinogenic, teratogenic and genetic effects

8.3.1 Carcinogenic effects

Epidemiological studies indicate an apparent causal relationship between skin cancer and heavy exposure to inorganic arsenic via medication, contaminated well water, or occupational exposure. Skin cancer as a result of arsenical poisoning is characterized by multifocal lesions over the entire body, especially in the palms and soles (Borgono, 1977; Ishinishi et al., 1977; Tsuchiya, 1977; Tseng, 1977).

Among the several types of skin cancer, epithelioma developing on the site of keratoses is the most common. The keratic lesions may exist for many years before they change to a malignant form of epithelioma which is usually of the squamous type. Basal cell carcinoma of a low-grade malignancy, in situ, accompanied by chronic "precancerous dermatitis" (Bowen's disease) is also found in cases of chronic arsenical dermatitis (Neubauer, 1946; Hill and Farring, 1948; Sommers and McManus, 1953; Roth, 1957; Braun, 1958; Fierz, 1965; Tseng et al., 1968; Nakamura et al., 1973).

The causal relationship between exposure to arsenical dust and lung cancer had not been confirmed by epidemiological observations until recently. Studies on hand now show a higher risk of lung cancer among workers exposed to arsenic trioxide in smelters and insecticide factories (Ott et al., 1974; Pinto, 1977). An increased relative frequency of deaths from lung cancer has been reported among vineyard workers (Ref7) and in the population exposed to arsenic in drinking water in Cordoba, Argentina (Bergoglio, 1964, cited by Wickstrom, 1972).

The development of tumors of other organs, frequently accompanied by skin cancers, has been reported in cases which were exposed to inorganic arsenic as medication, as an insecticide, as contaminated wine and in drinking water (Sommers and McManus, 1953; Roth, 1957; Braun, 1958; Bergoglio, 1964, cited by Wickstrom, 1972). However, the relationship between arsenic exposure and a higher risk of cancer in organs other than skin and lungs has not been confirmed (IARC, 1973). Nevertheless, it is important to note that hemangio endothelial sarcoma, often complicated by liver cirrhosis and splenomegaly, has been reported (Roth, 1957; Braun, 1958; Regelson et al., 1968; Popper and Thomas, 1975).

In spite of the epidemiological association between exposure to arsenic and cancer of the skin and lungs as well as angiosarcoma of the liver in man, a reliable and consistent induction of cancers in animals via arsenic exposure has not been achieved as yet (Hueper, 1966; IARC, 1973). A preliminary report by Osswald and Goerttler (1971) has suggested possible carcinogenic effects (induction of lymphoma) in mice which were exposed to several arsenical compounds by several routes.

8.3.2 Teratogenic effects

Teratogenic effects have been shown after a single administration of sodium arsenate to pregnant golden hamsters (Ferm and Carpenter, 1968; Ferm et al., 1971; Ferm, 1977). The dose of dibasic sodium arsenate was from 15 to 25 mg/kg body weight. The compound was given to the hamsters on the 8th day of gestation with intravenous injection (Ferm et al., 1971). Both the reabsorption and malformation rates in the fetus increased with increasing doses of the arsenate. The teratogenic effects were characterised by anencephaly, renal agenesis, and rib malformations. Similar teratogenic effects have been reported in mice (Hood and Bishop, 1972) at 25 mg/kg dose levels and in rats (Beaudoin, 1975) at 30 mg/kg dose levels. The comparative teratogenic effects of arsenate on rats and mice have been discussed in relation to protection by BAL (Hood et al., 1977).

8.3.3 Genetic effects

An increased incidence of chromosome abnormalities has been observed in lymphocytes of workers exposed to arsenic (Beckman et al., 1977) and patients therapeutically treated with arsenicals (Petres and Hagedorn, 1977). Arsenical interference with normal DNA repair processes has also been noted (Jung, 1969, 1971; Rossman et al., 1977) suggesting that damage to cellular genomes may occur through this mechanism.

8.4 Interaction between arsenic and other metals

According to Holmberg and Ferm (1969), sodium selenite (which is not teratogenic), when injected simultaneously with sodium arsenate, provided significant protection in an animal experiment against the malformations induced by arsenic.

Interactions between arsenic and selenium have also been described by Levander (1977). A study on the simultaneaus exposure to arsenic and lead revealed that this combination had additive effects on the levels of sulfhydryl groups, tissue respiration, and functional changes in the central nervous system in experimental animals (Novakova, 1969). Arsenical interactions with lead or cadmium have also been described by Mahaffey and Fowler (1977).

9. Dose-effect and dose-response relationships in chronic poisoning

The dose-effect relationship in chronic arsenic poisoning in Japanese infants may be estimated from the report by Hamamoto (1955) who observed that the victims ingested 90 to 150 g of dried milk per day which contained from 25-28 mg/kg of As_2O_3. They developed symptoms of arsenic poisoning, including pigmentation, swelling of the liver and anemia, when a total of about 115 mg of arsenic trioxide had been ingested. This means that these patients ingested an avurage of about 3.5 mg of arsenic trioxide daily over a period of 33 days. A total of 12,083 cases of poisoning with 128 deaths were reported as a result of this incident. Residual impairment of learning and of clinical function has been described among those who survived (Yamashita et al., 1972).

There is one report by Fierz (1965) concerning the dose-response relationship between skin cancer and the total dose of Fowler's solution ingested as medication. He reviewed 262 patients who had been treated for weeks or even for several years with Fowler's solution for various chronic dermatoses. Ten to 2600 ml of the solution were administered to the patients. Among those patients who developed late effects from this treatment, 40% had hyperkeratosis and 8% had skin cancer. A clear relationship between the increase in the incidence of both hyperkeratosis and cancer and the increased dosage of arsenic was indicated, as shown in Figure 2 (Fierz, 1965). The minimal dose of Fowler's solution for the development of hyperkeratosis was 60 ml and for skin cancer approximately 75 ml.

In areas in Cordoba, Argentina, in which chronic arsenic intoxication, the main symptoms being symmetrical palmar and plantar hyperkeratosis, has resulted from exposure to arsenic in drinking water, concentrations in the water have been variously reported as 2.8, 1.1, 3.8, and 4.5 mg As_2O_3/l (Wickstrom, 1972). For comparison, the national standard of 0.5 mg arsenite salt per liter drinking water may be mentioned.

In the arsenic polluted area in Czechoslovakia where nervous and respiratory effects have been observed the maximum concentrations of arsenic in drinking water were 0.070 mg/l and in surface water 0.210 mg/l (Somolnokyova, 1963, quoted by Wickstrom, 1972).

In the episode of arsenic poisoning reported in Taiwan, the dose-response relationship between skin cancer and arsenic concentrations in well water was described by Tseng et al. (1968). Out of the total population of 40,421, arsenical skin cancer was found in 428 people (10.6/1000 people). There were no patients under 20 years of age. The villages surveyed were divided into 4 groups according to the arsenic concentration in the well water (See Figure 3): (1) below 0.3 mg/l, (2) 0.3-0.6 mg/l, (3) above 0.6 mg/l, and (4) undetermined. It was estimated that the minimal amount of arsenic in well water necessary for inducing skin cancer was less than 0.29 mg/l.

There are a few reports regarding the dose-response relationship of chronic arsenic poisoning by inhalation and by occupational exposure. Pinto and McGill (1953) reported the relationship between the urinary arsenic level ranges and the percentage of dermatitis among workers exposed to arsenic trioxide. Out of those workers excreting 0.3 mg/l arsenic in urine, 35% suffered from arsenical dermatitis, while of those workers excreting 3.0 mg/l and above, all suffered from dermatitis. More studies are required in order to establish a dose-response and dose-effect relationship between the concentration of arsenic in air and in urine and the symptoms of arsenic poisoning.

10. Diagnosis, treatment, and prognosis

10.1 Acute poisoning

10.1.1 Inhalation

10.1.1.1 Diagnosis

Acute arsenic intoxication via inhalation usually does not occur except for acute arsine poisoning, although respiratory symptoms may occur among those who are suddenly exposed to high concentrations of arsenic in smelters. Acute skin lesions such as contact dermatitis may be observed around the eyes and mouth, as well as on the face and neck. The diagnosis of such cases is based upon the history of arsenic exposure. The measurement of arsenic in urine is useful provided the specimen is taken within a few weeks after exposure and provided no recent consumption of marine fish or shellfish has taken place.

10.1.1.2 Treatment and prognosis

A conservative treatment is usually applied to the skin lesions. British antilewisite (BAL) may be given in cases of severe symptoms of the respiratory system or the skin.

10.1.2 Ingestion

10.1.2.1 Diagnosis

The determination of arsenic in the hair, urine, blood, or stomach contents is useful for diagnosis if exposure to arsenic is not readily identified.

10.1.2.2 Treatment and prognosis

The treatment for acute arsenic poisoning by ingestion is referred to in medical textbooks, e.g. Krupp and Chatton's "Current Diagnosis and Treatment" (1974). Prognosis will depend upon both dosage and time of initiation of the treatment after ingestion. In some cases where recovery from acute poisoning has occurred, dermatitis and peripheral neuritis may persist for a relatively long time. The possible development of secondary liver impairment after acute or chronic poisoning has also been discussed (See Section 8.2.7).

10.2 Chronic poisoning

10.2.1 Diagnosis

In chronic arsenic poisoning, the differentiation between senile pigmentation, senile leukodermia, and arsenical dermatoses is extremely important for diagnostic purposes. The characteristics of the skin lesions resulting from arsenic poisoning have been described in Section 8.2.2. However, it is not necessarily easy to determine whether skin changes in older persons are of arsenical origin or are simply senile skin changes. This problem is especially evident in persons exposed to arsenic via ingestion.

Concentrations of arsenic in biological tissues may be within the normal range at the time a diagnosis is made. In such cases, a well-designed epidemiological study may be required if it is thought that a group of people might have been exposed to arsenic. The presence of white striae in the fingernails is a useful tool in the diagnosis of arsenical polyneuritis, because arsenic concentrations may be within normal limits during this condition (Heyman et al., 1956).

Recognition of damage to the upper respiratory tract, specifically perforation of the nasal septum, may be quite helpful for the diagnosis of chronic arsenic poisoning.

Liver damage, including such impairments as cirrhosis and angiosarcoma, which may be seen in the exposed person, may require differentiation in terms of the cause-effect relationship.

10.2.2 Treatment and prognosis

BAL has been used for the treatment of chronic arsenic poisoning, in particular in cases of dermatosis. Pinto and

McGill (1953) administered BAL to persons with arsenic dermatitis. They succeeded in augmenting the excretion of arsenic into the urine but not in improving skin changes such as melanosis and keratosis. Apart from the debatable treatment with BAL, the treatment of chronic arsenic poisoning may be mainly a conservative one.

Skin changes and neuropathy may be persistent over a long period of years. The skin changes seen in simple keratosis may progress into Bowen's disease, which will spread over the entire body in multiple forms.

11. Arsine

Arsine (hydrogen arsenide, AsH_3) is a colorless, inflammable gas with a slight garlic odor and is generated whenever nascent hydrogen is liberated in material containing arsenic. Since arsenic is present as a contaminant in many metal ores, the generation of arsine may occur in metal industries, nonferrous metal refineries, and in the manufacture of silicone steel, if these ores accidently come into contact with acid. It may also occur when the hydrogen ion is formed by hydrolysis, as in the reaction of moisture with a dross containing arsenic.

The toxicity and toxicological mechanism of arsine are quite different from those of other inorganic or organic arsenic compounds. Arsine is a well-known highly toxic gas and a powerful hemolytic poison in cases of both acute and chronic exposure.

Henderson and Haggard (1943) stated that the lethal dose of arsine for humans was 250 mg/kg for 30 minutes, and that poisoning symptoms would occur after a few hours of exposure to 3 to 10 mg/kg. Elkins(1959) reported a serious, nonfatal, acute case in a person who had worked in an atmosphere containing an average of 0.5 mg/kg arsine. Five workers, reported by Kipling and Fothergill (1964), developed typical arsine poisoning from exposure in a plant where an acetylene-like odor was detected during the slag-dissolving process in the rotating drum. The concentration of arsine in this factory was 5 mg/kg.

Morse and Setterling (1950) studied 2 fatal cases of arsine poisoning where aluminum had been used to remove arsenic. The concentration of arsine in this instance was 70 to 300 mg/kg.

Arsine poisoning is characterized by nausea, abdominal colic, vomiting, backache, and shortness of breath, followed by red urine and jaundice (Kipling and Fothergill, 1964). According to Bulmer et al. (1940), the following symptoms occurred after various lengths of exposure to arsine: shortness of breath on exertion, general malaise, nausea, poor appetite, palpitation on exertion, and headache. In some groups of workers a tingling sensation in the feet, chills, garlic breath, changes in the complexion, weakness, vomiting, and drowsiness were observed. Jaundice was also recognized in some workers. Among workers with the longest exposure, anemia was present. Arsenic trioxide in urine was elevated in almost all groups of workers, ranging from 0.04 to 4.3 mg/l. Even after the workers had left the arsine-contaminated area, arsenic trioxide in urine ranged from 0.04 to 0.1 mg/l. Peripheral neuritis was also reported by Dudley (1919). Liver disturbances may also accompany poisoning. In most fatal cases renal failure due to blockage of the renal tubules by hemoglobin casts seems to be the usual cause of death (Fowler and Weissberg, 1974). Residual functional impairment of the kidneys has been reported in one person following an acute episode of arsine poisoning (Muehrcke and Pirani, 1968).

The use of BAL for arsine poisoning is not promising, but symptomatic therapy is more reliable, particularly in the treatment of anuria. Blood transfusions may be necessary for severe anemia. Arsine toxicity and treatment have been recently reviewed (Fowler and Weissberg, 1974).

Table 1. World Production of Arsenic from 1911-1970 (From Ferguson and Gavis, 1972).

Decade	Average Yearly Production Metric Tons
1911-1920	12,600
1921-1930	21,700
1931-1940	39,400
1941-1950	44,000
1951-1960	34,400
1961-1970	42,700*

* Excludes U.S. production

Table 2. Arsenic Concentrations in some Foods not Sprayed with Arsenicals in the USA and Japan (Compiled from Schroeder and Balassa, 1966, and Nakao, 1960, respectively).

	Concentration of arsenic mg/kg wet weight
Food in USA	
Winter rye	2.40
Corn	0.00
Barley	0.85
Spinach	1.10
White onions	0.18
Tomatoes	0.00
Green beans	0.09
Wheat*	0.17
Corn*	0.11
Tomatoes*	0.10
Food in Japan	
Rice	0.033-0.045
Rice without bran	0.027-0.036
Wheat	0.020-0.034
Beef	0.100-0.190
Pork	0.135-0.205
Whale meat	0.150-0.250
Eggs	0.008-0.012
Gray mullet	0.325-0.585
Tuna fish	0.315-0.585
Red snapper	0.310-0.425
Sardine	0.390-0.550
Apple	0.020-0.022
Grape	0.015-0.075
Pear	0.012-0.073
White onions	0.005-0.033
Spinach	0.000-0.030
Tomatoes	0.007-0.012
Milk	0.002-0.017
Dehydrated milk	0.008-0.037

* Commercially available vegetables and grains

Table 3. Arsenic Concentrations in Human Organs and Tissues in Scotland and Japan (Compiled from Liebscher and Smith, 1968, and Kadowaki, 1960, respectively).

Tissue/Organ	Arsenic concentration mg/kg dry weight	
	Scotland	Japan
Adrenal	0.029	
Aorta	0.035	
Whole blood	0.036	
Bone	0.053	0.118 (femur)
Bone		0.074 (rib)
Brain	0.012	0.034
Hair	0.460	0.174
Heart	0.021	0.041
Intestine, large		0.025
Intestine, small		0.022
Kidney	0.026	0.041
Liver	0.034	0.042
Lung	0.078	0.047
Muscle	0.062 (pectoral)	0.029
Nail	0.283	0.892
Ovary	0.048	
Pancreas	0.047	0.020
Prostate	0.019	
Skin	0.080	0.064
Spleen	0.017	0.021
Stomach	0.022	0.022
Teeth	0.049	0.078
Thymus	0.019	
Thyroid	0.042	
Uterus	0.037	0.036

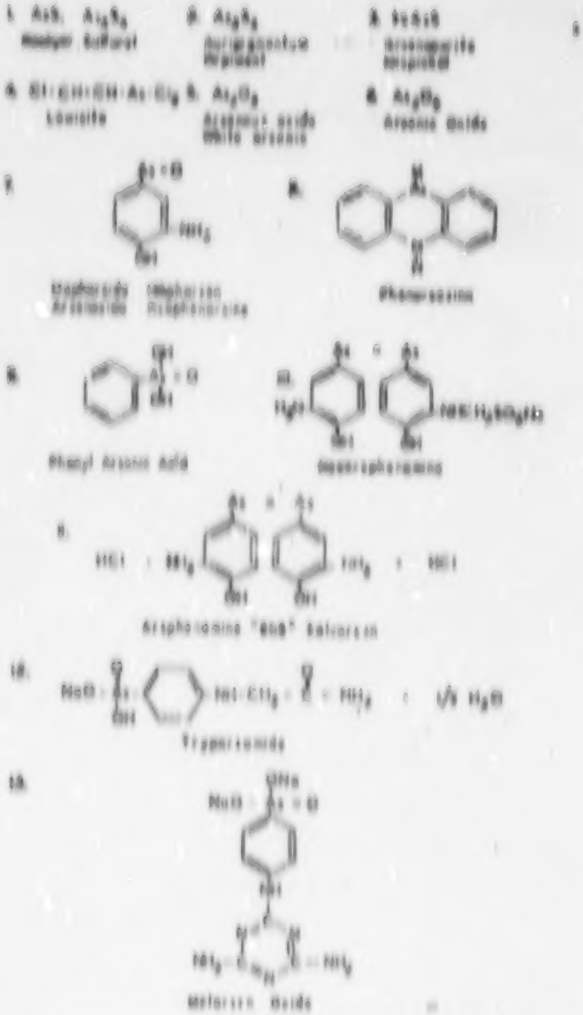
1. AsS, As2S2
Realgar Sulfurol
2. As2S3
Orpiment
3. FeAsS
Arsenopyrite
Mispickel
4. Cl·CH:CH·As·Cl2
Lewisite
5. As2O3
Arsenous oxide
White arsenic
6. As2O5
Arsenic Oxide
7.
Phenarsazine
9.
Phenyl Arsonic Acid
10.
Neoarsphenamine
11.
Arsphenamine "606" Salvarsan
12.
Tryparsamide
13.
Melarsen Oxide

Figure 1. Arsenicals with biologic action (From Vallee et al., 1960).

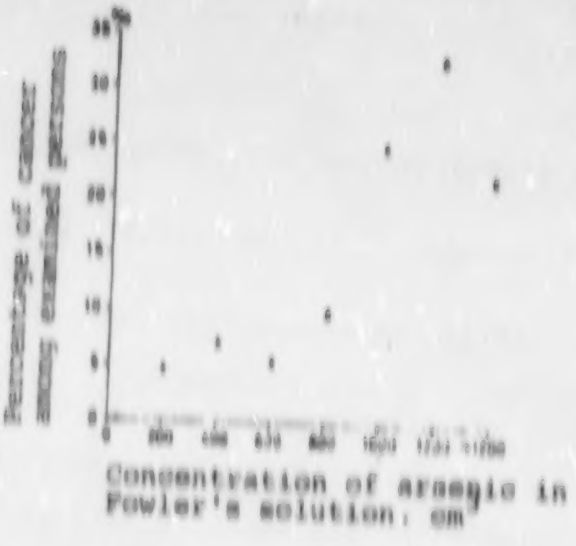

Figure 2. The relative frequency of skin cancer with increasing doses of arsenic (From Fiers, 1965).

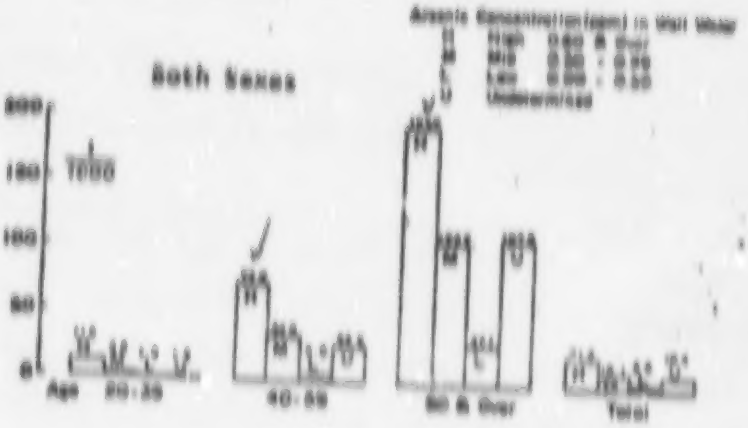

Figure 3. Age-specific and sex-specific prevalence rate (1/1000) for skin cancer arsenic concentration in well water (From Tseng et al., 1968).

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BARIUM

Andrew L. Reeves

1. Abstract

Soluble forms of barium are readily absorbed after inhalation. After ingestion barium sulfate remains essentially unabsorbed. Soluble barium salts such as barium chloride are absorbed to 10–30 % in hamsters. After absorption barium accumulates in the skeleton. An accumulation also takes place in the pigmented parts of the eye.

Poisoning with soluble barium compounds has resulted from accidental or suicidal ingestion. The Ba^{++} ion is a muscle poison, causing gastrointestinal, cardiac, and skeletomuscular stimulation followed by paralysis. In Szechuan province of China, a subacute form of barium poisoning ("pa-ping") was endemic due to use of contaminated table salt.

The mechanism of action of barium is based on its physiological antagonism to potassium, and cases of barium poisoning are accompanied by severe hypokalemia. Potassium infusion is an effective antidote.

Inhalation of barium sulfate dust causes a benign pneumoconiosis ("baritosis") with conspicuous radiographic manifestations but no impairment of pulmonary function. The condition has been reproduced in rats.

The primary route of exposure for the general population is usually via food.

Reviews on barium toxicology and metabolism have been written by Schroeder et al. (1972) and Marshall et al. (1973).

2. Physical and chemical properties

Barium, Ba, atomic weight 137.3; atomic number 56; density 3.5; melting point 725°C; boiling point 1,640°C; crystalline form yellowish-silver metal; oxidation state 2. The compounds to be taken up here are barium chloride, barium sulfate, barium carbonate, barium nitrate, barium sulfide, barium acetate, barium hydroxide.

Barium is the heaviest of the stable alkaline earths. The free element oxidizes readily in moist air and reacts with water or with dilute acids under evolution of hydrogen gas.

In its compounds, barium is a colorless divalent positive ion. Barium sulfate is one of the least soluble compounds known, in any medium. Volatile compounds of barium (especially halide salts) give the Bunsen flame a pale green color.

3. Methods and problems of analysis

Determination of barium with conventional analytical reagents is unsatisfactory for micro-quantities. Procedures in current favor include neutron activation analysis, limit of detection about 1 mg/kg (Bowden and Stitch, 1957); emission spectrography, limit of detection about 0.1 mg/kg (Gabrowski and Unice, 1958); and atomic absorption spectrophotometry, limit of detection about 0.01 mg/kg (Edelbeck and West, 1970). Several of these are specifically adapted for assay in biological material.

4. Production and uses

4.1 Production

Barium occurs chiefly as the mineral barite. Much smaller amounts are also mined as witherite. The United States, the Federal Republic of Germany, and the Soviet Union are the leading producers, the total world production being in the range of 4 million tons per annum. For the manufacture of barium chemicals, barite is reduced to the much more reactive barium sulfide through high-temperature sintering with charcoal. Similar treatment converts witherite to the water-soluble barium oxide.

4.2 Uses

In recent years, about 80 % of ground and crushed barite sold has been used directly as a weighting agent in oil- and gas-well drilling muds.

The remainder of barite and all witherite are used in the manufacture of glass, ceramics, television picture tubes, brick and tile refractories, plastic stabilisers, railroad flares, fireworks, fine chemicals, lubricating oil additives, permanent magnets, as well as in sugar refining, paper coating, steel hardening, and as pigment in paint (lithophone).

Barium-containing household and consumer products constitute a minuscule part of barium consumption, but have the greatest toxicological significance. They include rodenticides, insecticides and depilatories.

5. Environmental levels and exposures

5.1 General environment

5.1.1 Food and daily intake

Barium content in edible crops ranges from about 10 mg/kg in wheat and corn grain to several thousand mg/kg in brazil nuts (Beeson, 1941). Generally, barium content of food parallels calcium content, in a ratio of $1:10^2-10^5$. Expressed as mg Ba/kg Ca, typical values in milk were 45-136; wheat flour contained 1300 and oatmeal, 2320-8290 mg/kg (Henderson et al., 1962).

In an American hospital diet the daily intake of barium was estimated at 0.375 mg while in the diet of the general population it may be as high as 1.33 mg (Schroeder et al., 1972). Grummitt (1961) estimated that average dietary barium intake originated 25 % from milk, 25 % from flour, 25 % from potatoes and 25 % from miscellaneous high-barium foods consumed in minor quantities, especially nuts.

5.1.2 Water, soil, plants and ambient air

Barium constitutes about 0.04 % of the earth's crust, mostly confined to certain rock types. Agricultural soils contain Ba^{++} in the mg/kg range. Concentration of the element in sea water is 0.006 mg/l and in fresh waters, 0.007-15.0 (average 0.05) mg/l (Schroeder et al., 1972). Municipal waters of the United States ranged 0.0017-0.38 (average 0.043) and of Sweden, 0.001-0.02 mg/l (Bostrom and Wester, 1967). In urban air, the average concentration was 5 (range 0-1500) ng per m^3 in 18 U.S. cities (Schroeder et al., 1972).

Barium has been found in all biological material where assayed. Marine animals concentrate the element 7-100 times and marine plants 1000 times from sea water. Among land plants, oak, ash, Douglas fir, walnut, and particularly brasil nuts are the strongest accumulators of soil barium. Soybeans and tomatoes also accumulate soil barium 2-20 times (Robinson et al., 1950).

5.1.3 Cigarettes

Barium content of dry tobacco leaves was found as 88-293 mg/kg by McHargue (1913); more recent measurements yielded 24-170 (average 105) mg/kg (Voss and Nicol, 1960). Most of this barium content is likely to remain in the ash during burning. There are no values reported on smoke.

5.2 Working environment

The industrial uses of soluble barium are such that hazardous conditions from atmospheric contamination are uncommon. Hyatt (1971) has applied a limit of 0.5 mg Ba/m^3 for a number of years at the Los Alamos Laboratories with satisfactory results for the control of exposure to barium nitrate. It is not known what degree of added safety this limit incorporates.

6. Metabolism

6.1 Absorption

6.1.1 Inhalation

Soluble forms of barium are readily absorbed from all segments of the respiratory tract. Nasal absorption of $^{133}BaCl_2$ was estimated at 60-80 % of the dose at 4 hours after dosing (Cuddihy and Ozog, 1973) and alveolar absorption is of similar magnitude. According to measurements at tracer levels, even $^{131}BaSO_4$ was found to be cleared from the lungs, with a biological half-time of 8-9 days (Morrow et al., 1964). This indicated some solubility of $BaSO_4$ in body fluids, possibly in colloidal form.

Clearance of various forms of barium after inhalation exposure was studied by Einbrodt et al. (1972) and by Cuddihy et al. (1974). Different compounds of barium were cleared from the lungs in proportion to their solubilities; in the case of $BaSO_4$, the clearance rate depended on the specific surface area of the inhaled particles, and was lower for heat-treated than for untreated particles. Barium in fused montmorillonite clay had the lowest clearance rate.

6.1.2 Ingestion

Barium sulfate can be used as X-ray contrast material for gastrointestinal examinations, because during the relatively brief period of passage through the alimentary canal $BaSO_4$ remains essentially unabsorbed. Soluble barium salts do become absorbed, and in hamsters receiving $^{133}BaCl_2$ by intragastric intubation, absorption was 10-30 % of the dose (Cuddihy and Ozog, 1973).

Sutton et al. (1972) and Sutton and Shepherd (1973) found that addition of sodium alginate to the diet reduced intestinal absorption of barium in rats and man to 42-75% (average 64%) of control.

6.1.3 Parenteral administration

Thomas et al. (1973) measured the in vivo solubility of 4 barium salts after intramuscular deposition. Chloride and carbonate were about equally diffusible and left the injection site very rapidly. The sulfate showed a biological half-time of 26 days, and a fused aluminosilicate clay, 1400 days.

6.2 Transport and distribution

All alkaline earths have a tendency to accumulate in the skeleton, and the degree of osseous uptake for circulating barium was found to be 3 to 5 times that for calcium or strontium. Elsasser et al. (1969) found this preference for barium to be due to uptake on bone surfaces rather than to diffuse uptake. After intravenous injection of $^{133}Ba^{++}$ into beagle dogs, specific activity was highest in the sternum, followed by sacrum and coccyx, vertebrae, ribs, humerus and femur. In the skull, mandible, radius, ulna and tibia-fibula, the specific activity was less than whole-body specific activity.

In most soft tissues, barium accumulation after intravenous injection is slight and in proportion to their calcium content. An exception is the submaxillary gland of the rat which was found to concentrate barium from serum in preference to the other alkaline earths (Bligh and Taylor, 1962) and the eye, in which extremely high concentrations of barium are sometimes found (Bowden and Pirie, 1958). The pigmented parts of the eye (iris, sclera, and especially the choroid) are the strongest accumulators of circulating barium with concentrations reaching the 100 mg/kg (wet weight) level.

After inhalation exposure to 40 mg $BaSO_4/m^3$ 5 hours daily for 2 months, lymphatic transport was slight in rats. The skeletal concentration of Ba was 800-1,500 mg/kg dry substance (10-100 times the pulmonary concentration). Skeletal uptake decreased somewhat with advancing age (Einbrodt et al., 1972).

6.3 Excretion

Normal humans in a state of barium equilibrium (with virtually all of the intake occurring per os) excreted about 91 % of the total output in feces, 6 % in sweat and 3 % in urine (Schroeder et al., 1972).

Barium excretion at 3-6 hours after intravenous administration of a soluble salt was measured in saliva and seminal fluid of a healthy man, yielding values of 0.22-0.33 and 0.81 % of the dose, respectively (Harrison et al., 1967). In lactating cows, excretion in milk during the first 8 days after dosing was 0,6 % of an oral dose and 10 % of an intravenously administered dose (Turner et al., 1960).

7. Normal levels in tissues and biological fluids

Schroeder et al. (1972) published levels for barium in various organs of unexposed persons. The total amount in the skeleton of a 70 kg American adult was estimated at 2 mg/kg or about 90 % of total body barium. Other organs with measurable levels included the eye (330 µg/kg), lungs (160 µg/kg), connective tissue (125 µg/kg) skin (50 µg/kg) and adipose tissue (36 µg/kg). In other internal organs, barium concentration was slight. Among various parts of the eye, choroid had the highest barium level, reaching 600 mg/kg in the cow and 10 mg/kg in man (Bowden and Pirie, 1958).

Normal human blood contains 0.08-0.4 mg Ba/l (Gooddy et al., 1975); most or all is in the plasma fraction (Schroeder et al., 1972). Urinary excretion in unexposed persons averaged 26 µg Ba/day (Tipton et al., 1969).

8. Effects and dose-response relationships

8.1 Humans

Occupational intoxications with soluble barium salts are virtually unknown, but accidental or suicidal poisonings with barium-containing household and medicinal products have been reported. The compounds included the nitrate (Lydtin et al., 1965), sulfide (Jobba and Renyei, 1971; Gould et al., 1973) and carbonate (Morton, 1945; Maretic et al., 1957; Lewi and Bar-Khayim, 1964). In the Chinese province of Szechuan, an endemic condition resembling familial periodic paralysis ("pa-ping") has been described, which eventually turned out to be food poisoning from the very high proportion of barium in the table salt mined there (Allen, 1943).

The barium ion is essentially a muscle poison causing first stimulation and then paralysis. The symptoms usually begin with the gastrointestinal muscles and acute barium poisoning manifests itself rapidly after ingestion of a toxic dose, with nausea, vomiting, colic, and diarrhea. Skeletomuscular and cardiac symptoms follow with myocardial and general muscular stimulation and tingling of the extremities. Severe cases of poisoning progress to loss of tendon reflexes, heart fibrillation, and general muscular paralysis including the respiratory muscles, leading to death.

Electrocardiographic tracings of barium-induced cardiomyopathies were given by Sassine (1970) and Habicht et al. (1970).

Threshold of a toxic dose in adult humans is about 0.2-0.5 g Ba, lethal in untreated cases is 3-4 g Ba. These figures apply to the portion absorbed from the gut.

The barium ion is a physiological antagonist of potassium, and it appears that the symptoms of barium poisoning are attributable to Ba^{++}-induced hypokalemia. The effect is probably due to a transfer of potassium from extracellular to intracellular compartments rather than to urinary or gastrointestinal losses (Rosa and Berman, 1971). Serum potassium in acute cases of barium poisoning may decrease from the normal range of 3.5-5.0 m Eq/l to 1.5-3.0 m Eq/l, and the symptoms and signs are promptly relieved by intravenous infusion of K^{+} (Diengott et al., 1964; Berning, 1975).

Iatrogenic mishaps during the application of X-ray contrast materials have occasionally caused barium sulfate to enter the interstitial spaces and blood vessels, causing foreign-body granuloma or embolism, respectively. Inhalation of barium sulfate dust causes a pulmonary reaction with mobilisation of polymorphonuclear leucocytes and macrophages, and characteristic radiographic changes with dense, discrete, small opacities distributed throughout the lung fields ("baritosis"). However, the shadows appear to be due to the radiopacity of barium sulfate itself rather than to any tissue lesions, and the condition is symptomless with no abnormality of pulmonary function (Wende, 1956; Lévi-Valensi et al., 1966).

8.2 Animals

Long-term feeding studies in rats, with the drinking water containing 5 mg/l Ba^{++} (as acetate), caused no measurable toxic effects (Schroeder and Mitchener, 1975). Chickens were found to tolerate 1000 mg/l Ba^{++} in their diet; 2000 mg/l caused slight depression of growth; 4000 mg/l caused substantial depression of growth but no increase in mortality. The results were similar with barium hydroxide and acetate (Johnson et al., 1960).

The human symptoms and signs of barium toxicity have been well reproduced in animal experiments. The cardiomyopathies in dogs and guinea pigs included ectopic ventricular contractions, ventricular tachycardia, and, finally, ventricular fibrillation. The non-cardiac effects were salivation, diarrhea, hypertension, skeletomuscular paralysis and respiratory paralysis (Schott and McArdle, 1974). Infusion of barium chloride into anesthetized dogs produced all of the above, plus a prompt and substantial hypokalemia. Potassium administration prevented or reversed all of these effects except the hypertension which appeared to have a different etiology not connected to the Ba^{++}-K^{+} antagonism (Roza and Berman, 1971). In denervated cats, barium exerted a stimulant action on the adrenal medulla, attributed to an increase in the permeability of chromaffin cell membranes and resulting in release of catecholamines (Douglas and Rubin, 1964).

Baritosis from inhalation of $BaSO_4$ dust was successfully reproduced in rats (Heluss et al., 1973). The lack of fibrotic reaction was confirmed, and response was confined to accumulation of alveolar macrophages and a reversible hyperplasia of the bronchial epithelium.

9. Medical aspects

Treatment of poisoning by soluble barium salts may be preventive or curative. Preventive treatment entails inhibition of absorption, by administration of sodium sulfate or sodium alginate (Sutton et al., 1972; Sutton and Shepherd, 1973). Curative treatment entails counteracting the paralytic effect of the Ba^{++} ion on muscle, by intravenous infusion of a potassium salt (Diengott et al., 1964; Berning, 1975).

Prompt administration of a soluble sulfate (e.g. Glauber salt) causes precipitation of barium sulfate in the alimentary tract and thus stops intestinal absorption.

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BERYLLIUM

Andrew L. Reeves

1. Abstract

Compounds of beryllium are not readily absorbed from the gastrointestinal tract or skin; they tend to form insoluble precipitates at physiological pH. Trace amounts which circulate in blood or body fluids tend to accumulate in the liver on a short-term basis and in bone on a long-term basis. Urinary excretion is irregular and not useful as diagnostic criterion.

Inhaled beryllium has an initial pulmonary half-time of about 2-3 weeks, but a particulate residuum tends to remain in the lungs for long periods. There is also some accumulation in the tracheobronchial lymph nodes. Pulmonary deposition and clearance may come to an equilibrium. Chelation therapy for the purpose of enhancing excretion has been largely unsuccessful.

Exposure to compounds of beryllium has caused dermatitis, acute pneumonitis, and chronic pulmonary granulomatosis ("berylliosis") in humans. The dermatitis is of the allergic type with edematous lesions following contact with soluble salts, or with granulomatous ulcerations following the cutaneous imbedding of insoluble compounds. Acute pneumonitis followed inhalation of soluble salts in high concentration; typical attacks resolved with complete recovery within several months. The chronic granulomatosis is an insidious and slowly developing disease with considerable mortality. It is associated with inhalation of various types of beryllium compounds, especially the "low-fired" oxide (calcined at about 500°C), sometimes in very low concentrations. Occupational as well as "neighborhood cases are on record.

In animal experiments, inhalation of beryllium compounds also caused osteosarcoma in rabbits and pulmonary adenocarcinoma in monkeys and rats. There is no epidemiological confirmation to date that these conditions are also caused by beryllium in humans. Other conditions associated with oral or parenteral administration of beryllium to animals include osteosclerosis, rickets, liver and kidney necrosis, anemia, and adrenal imbalance.

Beryllium is an inhibitor of numerous enzymes, especially alkaline phosphatase. It also interferes with DNA replication. Beryllium-protein complexes formed in vivo are antigenic and provoke a cell-mediated immune response in guinea pigs as well as in man. The immune status appears to influence the development of pulmonary berylliosis in beryllium-exposed subjects.

Beryllium is a light metal widely used in fatigue-resistant alloys, nuclear reactors, space vehicle, missile parts, electronics and for other specialized purposes. Industrial as well as general environmental exposure may occur in connection with these uses.

Reviews on beryllium toxicology were written by Kimmerle (1966) and Tepper (1972). Pertinent symposium volumes are "Pneumononiosis - Leroy U. Gardner Memorial Volume" 1950 (Proceedings of the Sixth Saranac Symposium); and "Beryllium - Its Industrial Hygiene Aspects" 1966 (AIHA-USAEC monograph).

2. Physical and chemical properties

Beryllium, Be, atomic weight 9.0; atomic number 4; density 1.9 (at 20°C); melting point 1,278°C; boiling point 2,970°C; crystalline form gray metal, hexagonal; oxidation state 2. Compounds to be taken up here are beryllium oxide, beryllium sulfate, beryllium hydroxide, berylliun fluoride, beryllium chloride, beryllium citrate, beryllium phosphate, beryllium silicate and zinc beryllium silicate.

Beryllium is one of the lightest elements. It differs significantly from the other alkaline earths in that its oxide is amphoteric. In that regard, beryllium shows similarity to aluminum and the two metals have a number of other chemical properties in common.

Beryllium is the lightest of all solid and chemically stable substances. The metal has very high specific heat, heat of fusion, sound conductance, and stiffness-to-weight ratio. In alloys, it confers on other metals improved resistance to fatigue, vibration, and shock. It also has extreme hardness and resistance to corrosion, probably attributable to the thin film of beryllium oxide rapidly forming on the surface of bare metal upon exposure to air.

Cationic beryllium salts when dissolved in water undergo hydrolysis and the pH of these solutions is acidic: 3.7 for isoosmolar (0.154 M) beryllium sulfate (Reeves and Vorwald, 1961). At pH values between 5 and 8, the element tends to form insoluble hydroxides or hydrated complexes, and at pH values above 8, beryllates.

3. Methods and problems of analysis

At one time, widely used reagents were alkannin, naphthazarin, naphthochrome green G, and chrome azurol S. The limit of detection with these methods was 10-700 µg Be/l, but cumbersome preparatory procedures have rendered them obsolete. The same may be said of the method based on the fluorescent dye morin, which had a limit of detection of 0.02 µg Be/l.

Spectrographic methods include direct current arc (Cholak and Hubbard, 1952), alternating current arc (Keenan and Holtz, 1964) and alternating current spark (Smith et al., 1952). These have limits of detection in the range of 0.5-5.0 ng Be/sample. An atomic absorption spectrophotometric method has been described by Bokowski (1968), with a limit of detection of 40 µg/l. The most sensitive method for beryllium analysis is gas chromatography coupled with an electron capture detector (Frame et al., 1974) or a mass spectrometer (Wolf et al., 197[illegible].

4. Production and uses

4.1 Production

Most beryllium is present in localized deposits of beryl. The highly treasured gemstones, emerald and aquamarine, are colored variants of beryl. Other beryllium-containing minerals number about 30 and include such other semi-precious stones as euclas, phenakite and chrysoberyl. Most beryllium is mined as the mineral beryl; other sources are bertrandite and helvite. Total world production is presently at about 10,000 tons per annum. Leading producers are Brazil and the Soviet Union; other deposits are widespread around the world, including the U.S.A. and various countries in Africa.

The ores are first converted to beryllium hydroxide by roasting or sintering, leaching, and precipitation. Beryllium hydroxide is then (1) converted to fluoride and reduced with magnesium to obtain beryllium metal; (2) reacted with carbon and melted with copper to obtain the master alloy.

Beryllium oxide ("beryllia") is prepared commercially by calcining beryllium hydroxide at temperatures ranging from about 500 to 1750°C. There is ample evidence that all chemical reactivity, including toxicity, of beryllium oxide is inversely related to the temperature of firing (Spencer et al., 1965). This correlation is apparently due to differences in crystallite size.

4.2 Uses

About 20% of world production is presently used as the free metal. Applications include missile and nuclear reactor components, rocket nozzles, aircraft brakes, electrical relays, space optics, space vehicle reentry cones, X-ray windows, inertial guidance parts, and a number of classified weapons parts. Beryllium alloys account for about 72% of the total production. The master alloy is 96% Cu, 4% Be. It can be remelted to obtain a family of dilute beryllium-copper alloys ranging from 0.5 to 2.75% Be. These are used as current-carrying springs, welding components, bearing sleeves, non-sparking tools and dies, and as underseas cable repeater and amplifier housing. A beryllium-nickel alloy is used in diamond drill bit matrixes, watch balance-wheels, and aircraft and spacecraft parts. The remaining 8% of beryllium produced is used as the oxide in ceramic formulations for resistor cores, integrated circuit chip carriers, and radio and laser tubes. An early major use of beryllia in fluorescent tube phosphors has now largely been abandoned.

5. Environmental levels and exposures

5.1 General environment

5.1.1 Food and daily intake

Petzow and Zorn (1974) have recently measured beryllium concentrations in food in Western Germany. They found in polished rice 0.08, in toasted bread 0.12, in potatoes 0.17, in tomatoes 0.24 and in head lettuce 0.33 mg Be/kg substance (dry weight basis). Total intake figures for beryllium have not been published, but may be estimated as around 100 μg/day of which only a minor fraction is intake by inhalation.

5.1.2 Water, soil, plants, ambient air and cigarettes

Beryllium occupies the 35th place in the terrestrial abundance list of elements and its overall concentration in the lithosphere is estimated at 5 mg/kg.

Ordinary agricultural soils and natural waters contain beryllium in the μg/kg or μg/l range. In birch, aspen and willow, beryllium content may rise as high as 3 mg/kg (Nikonova, 1967).

Early reports on "neighborhood cases" of pulmonary berylliosis at a frequency of 1-3% in the general population living within about a mile of the plant (Eisenbud et al., 1949) led to investigations disclosing that beryllium was emitted in the stack gases resulting in ambient concentrations of about 100 ng/m^3 around the plant. Average beryllium content of general urban air was reported by Sterner and Eisenbud (1951) as follows: Boston 0.3, New York 0.5, Brookhaven 0.7, Cleveland 1.3, and Pittsburgh 3.0 ng Be/m^3. Much of this probably originated from the burning of bituminous coal, which contains 0.1-3.0 mg/kg of beryllium.

In three brands of West German cigarettes, beryllium levels were 0.47, 0.68 and 0.74 μg/cigarette, with 4.5, 1.6 and 10.0% of the beryllium content, respectively, escaping into the smoke during smoking (Petzow and Zorn, 1964).

5.2 Working environment

Beryllium production in quantity commenced in the 1930's, and because of the early ignorance regarding its toxicity, no environmental controls were practiced until the late 1940's. Few measurements exist regarding the pre-1950 in-plant levels of beryllium to which workers were exposed, but they are retrospectively estimated as very high. Breslin and Harris (1959) reviewed early reports and concluded that inhalable beryllium in ore treatment rooms, around baking furnaces, in the neighborhood of lathes, or at the sites of fluorescent phosphor blending, milling, and salvaging, must have been around 1 mg/m^3.

In 1949, the U.S. Atomic Energy Commission, a major consumer of beryllium products, adopted the first occupational exposure standard at 2 μg Be/m^3 which in 1955 was adopted as the ACGIH threshold limit value. This resulted in substantial and widespread improvement of conditions, with average air concentrations in well-monitored plants dropping to below 2 and sometimes to as low as 0.1 μg Be/m^3 (Mitchell and Hyatt, 1957). In less well- monitored plants, breathing zone concentrations sometimes were appreciably higher. Locker room and shoe-change room facilities, as well as lunch rooms, frequently showed general air concentrations as high as regular production areas.

6. Metabolism

6.1 Absorption

6.1.1 Skin

Since most beryllium salts do not remain soluble at physiological pH, there is ordinarily no ready systemic diffusion following local contact. Ionic beryllium applied to the skin becomes largely bound to epidermal constituents, mainly alkaline phosphatase and nucleic acids (Bulman, 1969). Resorption of tracelevels of $^{7}BeCl_2$ through rat tail, with subsequent systemic distribution, was reported by Petzow and Zorn (1974).

6.1.2 Inhalation

Following intratracheal injection, $BeSO_4$ in trace amounts was either retained in the lungs of rats for long periods or mobilized after 16 days; ^{7}Be citrate (a soluble, non-ionizing complex) was completely mobilized after 4 days (VanCleave and Kaylor, 1955). $^{7}BeCl_2$ in the amount of 10 µCi showed a pulmonary half-time of 20 days; 18% of the dose accumulated in the bones in 147 days (Kuznetsov et al., 1974).

During inhalation exposure to $BeSO_4$, beryllium concentrations in the lungs of rats built up to an equilibrium in about 36 weeks and remained at a plateau for the balance of the exposure (Reeves et al., 1967). The inhalation concentrations determined the plateaus according to the following correlations: at 1.75 µg/m^3, about 2 mg/kg; at 17.5 µg/m^3, about 6 mg/kg; at 35 µg/m^3, about 9 mg/kg; at 175 µg/m^3, about 18 mg/kg.

Clearance of inhaled beryllium from the lungs of rats was multiphasic, each phase corresponding to a logarithmic function. Pulmonary beryllium content was approximately halved during the first 2 weeks post exposure; thereafter the clearance rate diminished rapidly and a residuum of the inhaled beryllium in the amount of 0.2-0.7 mg/kg, perhaps in incapsulated form, remained in the lungs for years.

6.1.3 Ingestion

Reeves (1965) measured absorption of ingested beryllium sulfate from the gastrointestinal tract of rats. At levels of 0.6-6.6 µg Be/day in the drinking water, about 80% of the intake passed the gastrointestinal tract unabsorbed. The remainder was probably absorbed from the stomach, the pH of which (about 3.0-3.6 in the rat) allowed the beryllium sulfate to remain in ionized condition. Upon entering the alkaline milieu of the intestine, the beryllium became precipitated as the phosphate and was excreted in the feces.

6.2 Transport, distribution, excretion, and biological half-time

The transport of beryllium in body fluids has been studied by Feldman et al. (1953), Reeves and Vorwald (1961), and Vacher and Stoner (1968a). The consensus of these studies is that the bulk of circulating beryllium is in the form of a colloidal phosphate, probably adsorbed on plasma α-globulin. Minor portions are carried as citrate or hydroxide. A complex with serum proteins is formed only at acidic pH and has, as transport form, no in vivo significance.

Vacher and Stoner (1968b) measured the removal rate after intravenous injection of $BeSO_4$ (radioactively tagged with $^7BeCl_2$) or of carrier-free $^7BeCl_2$ from rat blood. The biological half-time for the carrier-free form was about 3 hours; the clearance curves indicated biphasic removal, the second phase showing inverse relation of the rate to the dose. At higher concentrations, the beryllium ion formed phosphate aggregates, which were removed by the reticuloendothelial system (Vacher et al., 1974).

Circulating beryllium was carried to all tissues, and analyses following administration normally yielded measurable levels in most organs. On a short-term basis (2.5 hours after intravenous injection) organ distribution was dose-dependent, favoring the skeleton for smaller doses (< 50 µg Be/kg) and the liver for larger doses (up to 500 µg Be/kg). Hepatic beryllium appeared to be colloidal, and perhaps protein-bound. Beryllium became gradually mobilized from the liver of rats in the course of about 100 days and transferred to the skeleton; it apparently followed magnesium and became structurally incorporated into bone (Van Cleave and Kaylor, 1955). Part of the absorbed beryllium, variously estimated as 20-60%, was excreted in the urine. Plasma beryllium did not pass the glomerulus and the mechanism of excretion was tubular, with some damage inflicted upon the tubular epithelium in the course of secretion.

According to studies conducted on cows with radioactive beryllium, less than 30 mg/l of injected activity was recovered in the milk. The biological half-time in milk was 19 hours (Mullen et al., 1972).

7. Levels in tissues and biological fluids

7.1 Normal levels

In view of the increasing ubiquitousness of beryllium, it may be expected that biological specimens will in most cases contain detectable levels. In human pulmonary tissue, amounts less than 20 μg/kg (dry weight basis) are not regarded as indicative of occupational exposure. Blood and urine levels of unexposed persons (i.e. less than about 1 μg/l) were undetectable by the classic methods and determinations with the newer methods are yet to be made.

7.2 Biological indicators of exposure

Pulmonary levels of beryllium in occupationally exposed workers may be as high as 1-100 mg/kg dry tissue. Often, various segments of the same lung may exhibit widely differing levels. Beryllium in blood and urine is also variable, the levels in exposed persons being 0.02-3.0 μg Be/l (Lieben et al., 1966).

8. Effects and dose-response relationships

8.1 Local effects and dose-response relationships

8.1.1 Skin contact

8.1.1.1 Humans

Beryllium dermatitis was described by Van Ordstrand et al. (1945) as edematous papulovesicular lesions which appeared particularly on the exposed surfaces of the body of workers handling soluble beryllium salts. However, if insoluble beryllium compounds became imbedded in the skin, e.g. after injury with a fluorescent tube, necrotising granulamatous ulcerations followed which did not heal readily. Curtis (1951) recognised that the dermatitis was the allergic-eczematous type and developed a patch test. In 1955, Sneddon reported that a patient with a patch test positive to beryllium developed a sarcoid-like granuloma at the test site. Nishimura (1966) examined 111 cases of contact dermatitis, 11 cases of skin ulceration and 40 cases of conjunctivitis in a beryllium refinery and concluded that delayed allergy was responsible for acute beryllium disease. Epstein (1967) classified the skin reaction to beryllium as granulomatous hypersensitivity, and observed lymphocyte blast transformation (Hanifin et al., 1970) and macrophage migration inhibition (Henderson et al., 1972) in preparations originating from beryllium-sensitive subjects.

8.1.1.2 Animals

Dutra (1951) produced experimental beryllium granulomas in the skin of pigs which resembled the human lesion. Cutaneous sensitization of guinea pigs with soluble beryllium compounds was accomplished by Alekseeva (1965).

8.1.2 Inhalation

8.1.2.1 Humans

Acute pulmonary beryllium disease was first seen in beryllium extraction plants in Germany, Italy, the Soviet Union, and in the American state of Ohio. The cases resulted from inhalation of aerosols of soluble beryllium compounds, typically the fluoride, in relatively high concentrations. All segments of the respiratory tract were sometimes involved, with rhinitis, pharyngitis, tracheobronchitis, and pneumonitis. The acidity of beryllium salt solutions was the probable etiological factor and there appeared to be a definite dose-response relation both with respect to rapidity of onset and severity and duration of the inflammation (Van Ordstrand et al., 1943). The threshold of an injurious concentration (in mg Be/m^3) is about 30 for the high-fired oxide, 1-3 for the low-fired oxide, and 0.1-0.5 for the sulfate (Hall et al., 1950, Stokinger et al., 1950). Although there were some fatalities resulting from the acute syndrome, recovery after several weeks or months was the rule. No non-occupational cases have been observed.

8.1.2.2 Animals

Acute chemical pneumonitis following inhalation of beryllium sulfate was produced in a great variety of animals by Stokinger et al (1950). The fluoride ion had a synergistic effect on beryllium toxicity; alternate exposure to $BeSO_4$ and HF, or exposure to BeF_2 produced about twice as severe effects at any given beryllium concentration as those attributable to $BeSO_4$ alone.

Acute pneumonitis was also produced with insoluble beryllium compounds in 1950 by Hall et al., using different grades of beryllium oxide. High-fired BeO did not produce injury in most animals at concentrations of up to 30 mg Be/m^3. Low-fired BeO at about 1/10 of the former concentration caused mortality in rats and marked pulmonary damage in dogs in 10-40 days.

8.2 Chronic effects and dose-response relationships

8.2.1 Pulmonary granulomatosis ("berylliosis")

8.2.1.1 Humans

Hardy and Tabershaw (1946) described a chronic pulmonary condition among fluorescent lamp workers in Massachusetts. The character of this syndrome was quite different from that of the acute cases, with shortness of breath being the leading symptom. Pulmonary X-rays showed miliary mottling, and histopathological examination of lung tissue showed interstitial granulomatosis. The granulomas were composed of monocytes, surrounded by a zone of lymphocytes and plasma cells (Vorwald, 1948; Dudley, 1959).

Insoluble beryllium compounds, particularly the low-fired oxide, appeared to be most often involved in the causation of this condition. A dose-response relation between extent of exposure and severity of disease was emphatically absent, with workers from the cleanest plants and "neighborhood cases" sometimes showing the worst clinical forms (De Nardi et al. 1949; Sterner and Eisenbud, 1951; Hardy and Tepper, 1959).

The onset of berylliosis may be insidious, with only slight cough and fatigue which can occur as early as 1 year or as late as 25 years after exposure. Progressive pulmonary insufficiency, anorexia, weight loss, weakness, chest pain, and constant hacking cough characterize the advanced disease. Cyanosis and clubbing of fingers may be seen in about 1/3 of cases, and cor pulmonale is another frequent sequel. In past years, the mortality rate was nearly 30%, but after institution of corticosteroid treatment it has improved somewhat.

8.2.1.2 Animals

The granulomatous pulmonary lesions characteristic of the chronic disease in humans have been reproduced in animal models with only partial success. Policard (1950) reported nodular granulomata in the lungs of guinea pigs exposed to beryllium oxide, but the lesions regressed after the 40th day of exposure. Various lesions resembling in some measure the human type of chronic berylliosis, but also involving edema or emphysema, were produced in rats by intratracheal injection of beryllium oxide by Lloyd-Davies and Harding (1950).

8.2.2 Other chronic effects

8.2.2.1 Chronic effects on the skeleton

Guyatt et al. (1933) discovered beryllium rickets in poultry and other livestock fed beryllium salts at 0.5% dietary level. The condition was apparently caused by intestinal precipitation of beryllium phosphate and resultant decrease of plasma phosphorus levels. However, Sobel et al. (1935) found that the cartilage of rats fed a beryllium-containing diet would calcify only very imperfectly in vitro in solutions containing adequate concentrations of phosphate, the effect being attributable to inhibition of alkaline phosphatase.

Cloudman et al. (1949) demonstrated osteosclerosis in the long bones, pelvis, and skull of rats and mice injected with beryllium sulfate or zinc beryllium silicate. Marrow was replaced by spongy bone, causing disturbances of hematopoiesis with macrocytic anemia and decrease in the rate of hemoglobin biosynthesis (Stokinger et al., 1953).

Gardner and Heslington (1946) discovered osteosarcoma in rabbits after intravenous injection of zinc beryllium siliate. Similar results were obtained subsequently by others with a variety of beryllium compounds, including the oxide and phosphate. Occurrence of the tumors required 8-13 months after injection; their histological type was chondroblastic, osteoblastic, or fibroblastic.

8.2.2.2 Chronic effects on visceral organs and blood

Focal necrosis of the liver with progressive destruction of parenchymal cells was observed in rats following intravenous beryllium administration (Aldridge et al., 1950). Beryllium accumulated in the lysosomes and nuclei, and it was observed that dietary protein depletion protected the livers against the toxic effects of intravenous beryllium sulfate. Apparently, the site of attack of $BeSO_4$ on the cell became inaccessible after protein depletion (McLean and Witschi, 1966).

Mietkiewski and Malendowicz (1966) observed, after intraperitoneal injection of $BeCl_2$ into rats, enhanced excretion of steroid hormones from the adrenal cortex. Clary et al. (1972) considered adrenal imbalance a triggering factor in the development of chronic berylliosis.

Macrocytic anemia in dogs, rabbits, and rats was produced with beryllium fluoride. Both the newly formed intraerythrocytic protoporphyrin and globin were significantly decreased (Stokinger et al., 1953).

8.3 Carcinogenic effects

8.3.1 Humans

In 1952, a "Beryllium Case Registry" was established at the Massachusetts General Hospital, which accumulated the records of all reported cases of occupational and environmental beryllium exposure (Hardy et al., 1967). Mancuso (1970) has recently examined this material and other epidemiological sources, a total of more than 800 cases. It appears from this study that the prevalence of lung cancer among beryllium-exposed persons, in comparison to a control cohort, was not elevated. However, the prevalence of lung cancer did show positive correlation with the prevalence of preexistent pulmonary disorders, including berylliosis. On the other hand, incidence of pulmonary cancer among beryllium workers was inversely related to length of employment in the plant.

The presently available evidence is incomplete and allows contradictory interpretations regarding the carcinogenicity of beryllium in man. The Occupational Safety and Health authorities of the U.S.A., as well as Germany and Sweden, view beryllium as a potential human carcinogen, based essentially on the experimental animal evidence. Individual human case reports notwithstanding (Niemöller, 1963), there is as yet no convincing epidemiological evidence to support that view.

8.3.2 Animals

Inhalation exposure of rabbits to beryllium oxide at a concentration of 6 mg Be/m^3 (5 hrs/day, 5 days/week, for 48 weeks) produced osteosarcoma of the pubic bone with extension into the contiguous musculature and metatases to the lung (Dutra et al., 1951). Inhalation exposure of rats to beryllium sulfate at a concentration of 33 µg Be/m^3 (7 hrs/day, 5.5 days/ week, for 60 weeks) or intratracheal injections of BeO at a total dose of 338 µg Be (in saline) produced pulmonary adenocarcinomas with metastases to the tracheobronchial lymph nodes and pleura (Vorwald et al., 1955). Schepers et al. (1957) and Reeves et al. (1967) studied these tumors further and established that incidence of pulmonary adenocarcinoma in rats after inhalation exposure to beryllium sulfate at levels of 20-200 µg Be/m^3 was 100% after 13 months. Carcinogenic activity in the rat was confirmed for other beryllium compounds including the fluoride, phosphate, silicate, and for dust of beryl ore (Wagner et al., 1969). The tumors were of various histological types including acinar, papillary, mucigenous, and epidermoid. Pulmonary carcinomas were also produced in rhesus monkeys by Schepers (1964) and Vorwald (1968).

8.4 Mechanisms of toxic action

8.4.1 Effect on enzymes

The beryllium ion is the strongest known inhibitor of alkaline phosphatase and this inhibition is non-competitive. Belman (1969) showed that beryllium chemically combined with cutaneous alkaline phosphatase, and Reiner (1971) showed beryllium binding of *Escherichia coli* alkaline phosphatase. However, it is noteworthy that serum alkaline phosphatase activity in rats remained unaffected by inhalation exposure to beryllium sulfate (Reeves et al., 1967).

Beryllium also inhibits other phosphatases, notably phosphatidic acid, adenosine triphosphatase and β-glycerophosphatase. These enzymes are Mg^{++}- or K^{+}-activated, and the inhibition was in some cases competitive (Thomas and Aldridge, 1966).

Other enzymes which various concentrations of beryllium have been able to inhibit are phosphoglucomutase (Cochran et al. 1951), phosphoglyceromutase (Thomas and Aldridge, 1966), hexokinase and deoxythymidine kinase (Mainigi and Bresnick, 1969), lactate dehydrogenase of rabbit or sheep muscle or of rat lung homogenates (Schormuller and Stan, 1965; Reeves, 1967), malic, succinic, and α-ketoglutaric dehydrogenases in the livers and lungs of rats (Mukhina, 1967), nonspecific esterases in rat liver cells (Mietkiowski and Malendowicz, 1967), amylase in pancreatic tissue, saliva, serum, and urine (McGeachin et al, 1962), enolase (Malmström, 1955), hepatic acetanilide hydroxylase, aminopyrine demethylase, tryptophan pyrrolase, and aryl hydrocarbon hydroxylase (Witschi and Marchand, 1971).

8.4.2 Effect on protein and nucleic acid metabolism

The binding of beryllium to various proteins as a step in the elicitation of toxic action was first suggested by Aldridge et al. (1950), studied by Belman (1969), and recently reviewed by Reiner (1971). Although beryllium proteinates are not a substantial transport form in body fluids, they do form in situ in minute quantities and they may be antigenic (Krivanek and Reeves, 1972. Chevremont and Firket showed in 1951 that beryllium sulfate inhibited cell division in the metaphase, with marked decrease in the intensity of the Feulgen reaction for DNA. The effect was specific to DNA, with RNA biosynthesis remaining unaffected. Modes of interaction of the beryllium ion with DNA of various species were studied by Truhaut et al. (1968) who noted preferential accumulation of radioberyllium in the nuclei of regenerating rat livers, and increase of the sedimentation constant of DNA after contact with $BeSO_4$. However, Witschi (1970) showed that, while beryllium did inhibit the replication of DNA in regenerating rat livers, it did not become attached to DNA. Increased misincorporation of polydeoxyadenosylthymidine by micrococcal DNA polymerase during polymerisation was noted by Luke et al. (1975). The effect was associated with a strong inhibition of the 3'-5'exonuclease activity of the enzyme. The sum of present evidence indicates that beryllium is a specific inhibitor, or perhaps modifier, of events leading to DNA replication.

8.4.3 Effects on immune factors

The epidemiology of berylliosis cases was suggested as indicating the involvement of an immunological factor (Sterner and Eisenbud, 1951). Curtis (1951) concurrently developed a patch test. The patch test itself appeared to be sensitizing and was believed to be responsible for both dermal and pulmonary exacerbations of beryllium disease. It was consequently not used much as a diagnostic tool (Curtis, 1959). However, the phenomenon did indicate that beryllium was antigenic. Search for humoral antibodies was made (Pugliese et al., 1968; Resnick et al., 1970) but it now seems well established that beryllium hypersensitivity is essentially cell-mediated (Alekseeva, 1965). Passive transfer of hypersensitivity was accomplished in guinea pigs with lymphoid cells while the transfer of serum was ineffective. Chiappino et al. (1969) could inhibit all cutaneous reactions to beryllium in guinea pigs by injection of an antilymphocyte serum from rabbits. Inhalation exposure to beryllium sulfate could also suppress cutaneous reactivity (Reeves et al., 1972).

Mode of administration and choice of beryllium compound also influenced the nature of the immunological reaction. Vacher (1972) found only those forms and routes which were capable of producing a complex with skin constituents as immunogenic;

freely diffusible forms were "tolerogenic", including a very low dose of beryllium (4.78 µg/kg) intraperitoneally, or a high toxic dose (400 µg/kg) intravenously. Krivanek and Reeves (1972) showed that the beryllium ion acts as a hapten in provoking the immunological reaction. Complexes where the beryllium ion was unavailable (aurintricarboxylate, citrate) could not elicit sensitivity, whereas beryllium serum albuminate could elicit stronger sensitivity than the beryllium ion alone.

Methods for measuring hypersensitivity other than those related to skin response were developed recently. Among these, lymphocyte blast transformation (Hanifin et al., 1970) and macrophage migration inhibition (Henderson et al., 1972) appear promising. They were applied both to human clinical material (Deodhar et al., 1973) and to experimental guinea pigs (Marx and Burrell, 1973).

9. Diagnosis and treatment

9.1 Diagnosis

History taking is probably the most important diagnostic measure in the recognition of beryllium disease. All patients must have had at one time substantial exposure to beryllium, and it is now believed that the early "neighborhood cases" were all traceable to direct contact with a contaminated person or object rather than general air pollution (Radford and Tepper, 1967).

Beryllium in urine, blood, or pulmonary specimens helps to establish exposure but the concentrations have no relation to the severity of disease. In fact, in unaffected workers the levels may be as high as or higher than in patients with the acute or chronic disease (Lieben et al., 1966). It must also be remembered that some beryllium originating from general air pollution is invariably present in the lungs of most persons, especially city dwellers. The threshold of significant concentration is usually regarded as about 20 µg/kg dry weight.

The first finding in berylliosis is often an abnormal X-ray picture. Unfortunately, the observable densities are not typical for this disease, and their appearance in any case can be delayed for a year or more. Pulmonary function abnormalities may or may not parallel the development of X-ray changes. The basic lesion, when fully developed, is a decrease of diffusing capacity across the interstitial membranes, an "alveolocapillary block".

Patch testing (Curtis 1951; 1959) is not recommended as a diagnostic measure. It can give false positives as well as false negatives; it can be itself sensitizing, and was reported to cause flareups in dormant pulmonary lesions. Other tests based on hypersensitivity such as lymphocyte blast transformation or macrophage migration inhibition (Deodhar et al., 1973) may become useful adjuncts of diagnosis, but extensive experience is as yet lacking.

The most important problem of differential diagnosis is the distinction of beryllium disease from the sarcoidosis of Boeck and Schaumann, another chronic granulomatous inflammation of the lungs. The specific serological test for sarcoidosis, the Kveim test, is negative in berylliosis and other common complications of sarcoidosis including lymphadenopathy, ocular granuloma, uveo-parotid fever, peripheral neuropathy, hepatosplenomegaly, or leukopenia are rare or nonexistent in berylliosis. Other pneumoconioses, mycotic diseases of the lung, or miliary tuberculosis have sometimes been confused with berylliosis. The ultimate diagnostic proof is histopathological examination of pulmonary tissue which may be obtained by needle biopsy. Its results must be interpreted in concert with other test results discussed above.

9.2 Treatment

Corticosteroids, perhaps because of their immunosuppressive effect, are useful in arresting the inflammatory disease process (De Nardi, 1951). Chelating agents for removal of deposited tissue beryllium have been explored. Among these, aurintricarboxylic acid ("aluminon") proved effective in protesting mice and rats if given parenterally 1-8 hrs after intravenous injection of an otherwise lethal dose of beryllium sulfate. The chelate tended to accumulate in the kidneys and spleen (Schubert et al., 1952).

In the Soviet Union, aminoalkylpolyphosphinic acids were tried in animal experiments (Arkhipova et al., 1968). However, for the alleviation of chronic poisoning, chelating agents have proved thus far ineffective, and clinical trials were disappointing (Dequindt et al., 1973).

For beryllium implanted in the skin, the method of treatment is surgical.

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BISMUTH

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1. Abstract

Bismuth compounds are considered as poorly to moderately absorbed following inhalation or ingestion but there are no quantitative data. Absorbed bismuth is distributed throughout the soft tissues and bone, the highest concentrations being found in the kidney and liver. Bismuth passes through the placenta. Absorbed bismuth is excreted primarily via the urine. The biological half-time for the whole body retention is about 5 days but intranuclear inclusions containing bismuth seem to remain for years in the kidney of patients treated with bismuth compounds.

Bismuth is not essential either for man or animals.

High level exposure causes renal failure associated with degeneration and necrosis of epithelium of the renal proximal tubules, fatty changes and necrosis of the liver, reversible dysfunction of the nervous system, skin eruptions and pigmentation of the gums and intestine.

There are no reports on occupational exposures. For the general population the total intake from food is about 5-20 µg, with much smaller amounts contributed by air and water. An important source of exposure for specific segments of the population in the past was the therapeutic use of bismuth compounds. The cosmetic use still continues to be fairly widespread.

Short reviews on the toxicology of bismuth have been published by Browning (1969), Filepova (1971) and Avena (1974).

2. Physical and chemical properties

Bismuth, Bi, atomic weight 208.98; atomic number 83; density 9.7 (20°C); melting point 271.3°C; boiling point 1560±5°C; white crystalline metal with pinkish stain. Bismuth belongs to the Vb group of the periodic system together with arsenic and antimony. Its conductance in the solid state is only 0.48 of the liquid conductance, and it has the lowest thermal conductivity of all metals. Bismuth forms compounds in oxidation states +3 and +5. Of technological and toxicological interest are bismuth oxide, bismuth sulfide, bismuth oxychloride and salts of inorganic oxoacids (carbonate, nitrate, sulfate) and of organic acids (salicylate, triglycollate). Many of these salts have a basic form, such as basic nitrate or sub-nitrate. Bismuth forms trialkyls which are unstable in air but stable and insoluble in water (e.g. trimethyl bismuth).

3. Methods and problems of analysis

Atomic absorption spectrophotometry is an adequate method for the determination of bismuth in biological and environmental samples. Its limit of detection at 223.1 nm (air-hydrogen flame) is about 0.4 mg/l, and amounts as low as 1.5 µg can be determined in 1 g of tissue with a relative standard deviation of 5%. Biological samples should be wet-ashed with nitric, sulfuric and perchloric acids (Kinser, 1966; Hall and Farber, 1972; Delves et al., 1973). Spectrophotometry with dithizone has a detection limit of about 0.01 mg/l but lead interferes and has to be separated from bismuth (Pinta, 1970). Spark source mass spectrometry (SSMS) has been used recently for the determination of bismuth in human tissues; it has a limit of detection of 0.002 mg/kg wet weight (Hamilton et al., 1972/1973). There is not enough information to evaluate the accuracy of these methods.

4. Production and uses

4.1 Production

Bismuth occurs in native form and in minerals such as bismite (bismuth oxide) and bismuthite (bismuth sulfide) which is usually associated with sulfide ores of lead and copper and with tin dioxide. The production of metallic bismuth is linked to lead and copper refining. The current world production is about 4000-5000 tons, the main producers being Japan, Bolivia, Peru and Mexico. Pyrometallurgical separation of calcium-magnesium-bismuth drosses from which associated metals such as copper, lead and zinc are removed by suitable fluxes is a widely used technological process for the production of bismuth (Paone, 1970; Panel on Bismuth, 1970).

4.2 Uses

About 64.5% of bismuth is consumed in the United States as low melting alloys and metallurgical additives including electronic and thermoelectric applications. The remainder is used for catalysts, pearlescent pigments in cosmetics, pharmaceuticals and industrial chemicals (Panel on Bismuth, 1970).

A variety of bismuth compounds have been used as dusting powders, astringents, antiseptics, antacids and radioopaque agents in X-ray diagnosis (now replaced by barium sulfate). Another obsolete use is in the treatment of syphilis where bismuth compounds have been replaced by penicillin. Bismuth compounds that have been most widely used in therapy include bismuth potassium tartrate, basic carbonate, gallate, nitrate, salicylate and bismuth magma (suspension of hydroxide and basic carbonate suspension) (Panel on Bismuth, 1970).

5. Environmental levels and exposures

5.1 General environment

5.1.1 Food

Using pooled samples of food representative of the main regions of the United Kingdom, Hamilton and Minski (1972/1973) estimated the daily intake of bismuth as less than 5 µg (SSMS). The concentrations in individual dietary samples were not reported. According to Woolrich (1973) the daily intake from food and water is about 20 µg but again data on concentrations of bismuth in specific food items were not given. This estimate agrees with the model value for daily balance of elements in the reference man (ICRP, 1975).

5.1.2 Ambient air, water, soil and rocks

The concentrations of bismuth in urban air range from 1 to 56 ng/m^3, and in rural air from 0.1 to 6.6 ng/m^3 (Division of Atmospheric Surveillance, 1972). The concentration of bismuth in respirable fly ash (ADD<5 µm) was found to be about 4-5 g/kg (Davison et al., 1974). The daily intake of bismuth via inhalation is estimated as <0.01-0.76 µg (Woolrich, 1973; ICRP, 1975).

Concentrations of bismuth in drinking water have not been reported. Sea water contains about 0.2 µg Bi/1 (Environmental Studies Board, 1972).

Bismuth levels in soil are about 1 mg/kg, and in rocks from 0.1 mg/kg (coal) to 3 mg/kg (sandstones) (Bowen, 1966).

5.1.3 Pharmaceuticals and cosmetics

Pharmaceuticals and cosmetics are still a source of exposure to bismuth compounds for specific groups of the general population.

5.2 Working environment

Exposure to bismuth and some of its compounds may occur in the production of metallic bismuth and in the manufacture of pharmaceuticals, cosmetics and industrial chemicals but no reports are available on such exposure.

6. Metabolism

6.1 Absorption

Bismuth compounds are considered to be slightly to moderately absorbed through the respiratory and gastrointestinal tracts, depending on their solubility, but there are no quantitative data. Absorption through the skin is of interest in relation to the use of bismuth compounds in oil-based cosmetics but again there is no quantitative information (Sollman et al., 1938; Sollman and Seifter, 1939).

6.2 Distribution

Four days after i.m. injection of BiOCl or BiO(OH) to rats, 14.4% of the dose was found in the kidney, 6.6% in the liver, 1.5% in bone, 0.6% in muscle and less than 0.1% in blood. Seventeen days after administration only 0.6% remained in the kidney (Durbin, 1960). Two hours after i.v. injection of bismuth citrate and sodium bismuth thioglycollate to dogs and rabbits, about 3-5% of the dose was found in the kidney, 6-10% in the liver and 0.4% in the lungs. Within 24 hours the relative concentration in the kidney increased to 7-10%, and in the liver it decreased to 1-4%. Within one week, the concentration in the kidney and liver was reduced to 2.5%. After 4-5 weeks the liver concentration was again higher (1%) compared to the kidney (0.45%) (Sollman and Seifter, 1942).

The autopsy distribution of bismuth in 22 patients who received therapeutic i.m. injections (mainly bismuth salycilate) was as follows (median values, mg/kg, wet weight): kidney 33.3; liver 6.8; spleen 1.6; colon 1.2; lung 0.9; brain 0.6 and blood 0.5 (Sollman et al., 1938).

6.3 Excretion

Ingested bismuth is largely eliminated unabsorbed in feces. Model values for the daily balance of bismuth in reference man are - dietary intake 20 µg; fecal elimination 18 µg; urinary excretion 1.6 µg (ICRP, 1975).

Absorbed bismuth is mainly exureted in urine. The rate of excretion of bismuth following i.m. injection into rabbits of 13 different compounds was studied by Kolmer et al. (1939). Water soluble compounds were excreted more rapidly than those suspended or dissolved in oil. Excretion in four days varied from 82.1% of the dose for aqueous solution of bismuth thioglycollate to 1.9% for oil suspension of bismuth oleate but the excretion continued for at least 36 days. Durbin (1960) compared the excretion of elements of group V in rats following i.m. injection of soluble compounds in oxidation state +3. The metabolism of radiobismuth closely resembled the metabolism of UO_2^{2+} suggesting that Bi(III) was in an oxygenated or "basic" form. The retention in the kidney was short and by the 17th day after injection 95% of the dose had been excretud.

The permeability of the placenta to bismuth was demonstrated by Leonard and Love (1938) following i.m. injection of potassium bismuth tartrate and sodium potassium tartro bismuthate into pregnant rabbits and cats.

6.4 Biological half-times

ICRP (1960) adopted the following model values for the biological half-times of bismuth in man: whole body retention 5 days; kidney 6 days; liver 15 days; spleen 10 days and bone 13.3 days.

7. Normal values in tissues and biological fluids

The concentrations of bismuth in healthy human tissue in the United Kingdom were recently reported by Hamilton et al. (1972/ 1973), using SSMS. The highest mean concentration (400 µg/kg wet weight) was found in the kidney, followed by the bone (<200 µg/kg). The brain, lung and lymph nodes contained bismuth in concentrations from 10-40 µg/kg. Concentrations in the range from 2-8 µg/kg were found in the testis, blood, muscle, liver and basal ganglia. 95% of bismuth concentrations in normal lung and lymph node tissue (150 samples) were below 40 µg/kg, dry weight (SSMS; Brown and Taylor, 1975).

8. Effects and dose-response relationships

Bismuth is not an essential element, either for man or for animals.

8.1 Local effects and dose-response relationships

8.1.1 Animals

Application of trimethyl and triethyl bismuth to the skin of rats and rabbits has been reported to produce intense inflammation and edema. Local necrosis at injection sites was also observed. Acute local effects of inhalation of trimethyl bismuth by rats, cats and dogs include pulmonary edema. Eye irritation is another local effect observed in inhalation exposures to alkylbismuth (Sollman and Seifter, 1939).

8.1.2 Humans

Application of trimethyl bismuth to intact human skin produced no marked effects but intense irritation was noted if the skin had been scratched. Irritations of the upper respiratory airways and of the eye were also observed (Sollman and Seifter, 1939).

8.2 Systemic effects and dose-response relationships

The main systemic effects of bismuth compounds both in man and in animals are exerted on the liver and kidney.

8.2.1 Animals

8.2.1.1 Liver

Cloudy swelling with nuclear degeneration and occasional small foci of necrosis in the liver were observed in rabbits after lethal injections of sodium and potassium tartro bismuthate (i.v. 10-30 mg/kg; i.m. 150-350 mg/kg) and bismuth trioxide (i.m. 450 and 500 mg/kg) (Lucke and Klander, 1923). After six months, peroral treatment of rats and rabbits with potassium bismuthate (2.5, 0.25, 0.025 and 0.05 mg/kg) and bismuth sulfate (1.0, 0.5, 0.05 and 0.025 mg/kg) produced dilatation of intertrabecular capillaries, vascular stasis, and marked dilatation and congestion of the vessels. The hepatic tissue contained large irregularly shaped foci of reticuloendothelial cells. The severity of these changes was closely related. The activity of succinic dehydrogenase in the liver and of cholinesterase in the serum and liver was reduced even at doses of 0.025 and 0.05 mg/kg. Hepatic excretory function was abnormal in rabbits (bromsulfthalein retention). There were no effects when animals were given 0.005 µg/kg potassium bismuthate and 0.025 mg/kg bismuth sulfate (Seljankina et al., 1970).

8.2.1.2 Kidney

Kidney damage was produced in rats by single i.m. injections (0.03 to 1.5 g/kg) of 13 different bismuth compounds. Histological examination of 104 rats showed that 36 of 37 animals that died before 21 days had nephritis of varying degree of severity as had 11 of 67 surviving rats. The site of major effects was the proximal convoluted tubules. The least toxic was bismuth thioglycollate, doses of 0.04-0.080 g/kg producing severe nephritis (Kolmer et al., 1939). Following subcutaneous injections (5 g of bismuth subnitrate each day for 3 days), degenerative changes and intranuclear and intracytoplasmic inclusions appeared in renal proximal tubules of rabbits (Beaver and Burr, 1963a). These inclusion bodies are pathognomonic for bismuth exposure (Fowler and Goyer, 1975). Hemorrhages in the cortical and cerebral layer of the kidney and lympho-histiocystic infiltrations were found in rats after 6 months of peroral treatment with potassium bismuthate and bismuth sulfate (0.025-5.0 mg/kg) (Seljankina et al., 1970).

8.2.1.3 Nervous system

Immediately following inhalation exposure to trimethyl bismuth (10-20 min., concentration not stated) cats and dogs showed ataxia, restlessness and convulsive seizures. Between attacks the animals were depressed. Within about 24 hours they developed signs of severe encephalopathy (Sollman and Seifter, 1939). Disturbances in conditioned reflexes occurred in rats and rabbits treated with potassium bismuthate (ingestion, 2.5, 0.25 and 0.025 mg/kg) and bismuth sulfate (ingestion, 5.0 mg/kg) (Seljankina et al., 1970).

8.2.1.4 Other systemic effects

Blood pressure of dogs receiving hypodermic or intramuscular injections of trimethyl bismuth (4 doses, 350 mg/kg body weight) sank progressively to shock level without significant change of heart rate, arythmia or block. The animals were anesthetized with barbiturates (Sollman and Seifter, 1939). Intravenous injection of elemental bismuth (0.50 mg/kg) caused slight decrease in blood pressure and in amplitude and heart rate. Higher doses (1.8 mg/kg) resulted in heart block, and all fundamental functions of the heart were affected, including excitability, conductivity and contractility (Mason, 1927).

8.2.2 Humans

Although bismuth compounds had been extensively used for the treatment of syphilis and for other therapeutic uses, Beerman (1932) compiled only 22 fatalities as resulting from such therapy. Delayed deaths were mainly attributable to the involvement of the gastrointestinal tract, the liver or the kidney or a combination of two or all three of these systems. Deaths of 11 children occurred within 2-5 days following the use of suppositories containing bismuth salt of heptadiencarboxylic acid, and were preceded by vomiting, drowsiness, pain in the abdomen, convulsions and coma (Weinstein, 1947). There are no reports on the occupational exposure effects of bismuth (Filipova, 1971). No effects were observed in 13 normal human volunteers receiving about 450 mg Bi daily (as "bistrimate" - $C_{24}H_{28}O_{25}N_4BiNa_7$) from a few days to over a year (Lehman and Fassett, 1947).

8.2.2.1 Liver

An instance of jaundice with liver damage was reported in a 6-year child who received 4-5 mg/kg body weight of bismuth thioglycollate in a single injection. On the basis of this and a number of fatal cases reported by other authors Karelitz and Freeman (1951) concluded that soluble bismuth compounds are definitely hepatotoxic to man, producing fatty degeneration of the liver. This confirms the analysis of Beerman (1932) and Wolman (1940). Jaundice indicative of hepatitis occurred in 10.3% of 1032 persons treated for syphilis with bismuth compounds between 1932 and 1942 (Kulchar and Reynolds, 1942).

8.2.2.2 Kidney

Acute renal failure can occur following oral or parenteral administration of bismuth compounds such as bismuth sodium triglycollamate or thioglycollate, particularly in children (Boyette, 1946; Urizar and Vernier, 1966). The tubular epithelium is mainly affected with little change in the glomeruli. In 30 cases of bismuth nephropathy reviewed by Urizar and Vernier, the interval between medication and onset of symptoms and signs ranged from 6-7 weeks (mainly bismuth sodium thioglycollate, i.m. doses 5-200 mg; oral, 1.5-19 g). Functional alterations in acute bismuth nephropathy include severe depression of glomerular filtration rate, renal plasma flow, and proximal tubular reabsorption, as indicated by glucosuria, phosphaturia and aminoaciduria (Czerwinski and Ginn, 1964). Bismuth inclusions were found in the renal tubular epithelium of 12 of the 14 patients treated parenterally with bismuth compounds (Beaver and Burr, 1963b).

8.2.2.3 Neurological effects

A neurological syndrome possibly associated with bismuth subgallate ingestion and characterised by confusion, tremulousness, clumsiness, myoclonic jerks and gait disturbance was observed in four patients (Burns et al., 1974). Robertson (1974) also described similar neuropsychiatric symptoms and signs in 4 geriatric patients administered large doses of the same compound orally for several months.

8.2.2.4 Skin and mucosa

Pityriasis rosea-like eruptions and other skin manifestations such as the "erythema of the ninth day" syndrome have been occasionally described as a result of therapy with bismuth compounds (Goldman and Clarke, 1939; Dobes and Alden, 1949). Ulcerative stomatitis has been observed following bismuth therapy (Peters, 1941; Silverman, 1944). Bismuth pigmentation has been found in the colon, vagina and the skin (Heyman, 1944).

8.2.2.5 Other effects

Colitis, gastrointestinal bleeding, purpura, agranulocytosis and aplastic anemia have also been reported as resulting from administration of bismuth compounds (Avena, 1974).

8.3 Carcinogenicity, teratogenicity and mutagenicity

There is no evidence of carcinogenicity or mutagenicity of bismuth compounds, although bismuth penetrates the placenta (Leonard and Leve, 1979). No teratogenicity has been reported.

9. Treatment of bismuth poisoning

According to Avena (1974), dimercaptol (BAL) brings good results if given early. Other measures include atropine and meperidine to relieve gastrointestinal discomfort. Caution is required in fluid administration during anuric and oliguric phases of nephrosis, but loss of fluid and electrolytes should be covered in the subsequent diuric phase (Karelitz and Freedman, 1951).

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CADMIUM

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1. Abstract

About 5 % of ingested cadmium is absorbed by human beings, but calcium deficiency may increase this amount. The portion of inhaled cadmium absorbed is dependent on particle size and solubility. Absorbed cadmium is mainly stored in kidneys and liver. The excretion is slow, less than 0.01% of the total body burden per day, which corresponds to a biological half-time of more than 20 years in human beings. In liver and kidneys cadmium is mainly bound to the low molecular weight protein - metallothionein - which also might be the transport protein for cadmium and ultimately responsible for the prominent accumulation of cadmium in the renal cortex. The placental barrier is effective against cadmium and the newborn is practically free from this metal. There is a considerable accumulation with age, the mean kidney concentrations at age 50 being from 15-50 mg/kg wet weight in European countries, and USA, whereas considerably higher "normal" values have been found in Japan.

Ingestion of highly contaminated food or drink gives acute gastrointestinal effects. Excessive exposure to cadmium via inhalation may cause acute or chronic lung disease and chronic renal disease. The latter can also appear after long-term exposure via food. The renal damage is primarily a reabsorption defect in the proximal tubules, and the first sign of chronic cadmium intoxication is the appearance in urine of low molecular weight proteins - tubular proteinuria. Aminoaciduria, glucosuria and phosphaturia may occur later. Disturbances in mineral metabolism may cause mineral depletion in bone and osteomalacia has been found both in industrially exposed workers and in women exposed to excessive amounts of cadmium in rice - the latter disease being called the Itai-itai disease. Anemia and disturbed liver function may also result from excessive cadmium exposure.

Exposure to cadmium causes changes in the distribution and metabolism of zinc and some of the toxic effects of cadmium are thought to be due to the interference of cadmium with zinc enzymes

Exposure to cadmium concentrations in air around 50-100 µg/m^3 for a few years has given rise to emphysema and renal tubular disorders. In the general population the main exposure to cadmium is via food and long-term exposures with daily intakes of 300-480 µg have been estimated to cause renal tubular dysfunction. This estimate was based on cadmium concentration in rice. When data on fecal excretion of cadmium were used instead, a daily intake of around 200 µg was found. This is in accord with estimations based on a metabolic model for cadmium and a critical concentration in sensitive individuals of about 200 mg cadmium/kg wet weight in the renal cortex. WHO (1977) has recently stated that the critical level may be between 100 and 300 mg/kg with 200 mg/kg being the most likely estimate.

In order to detect renal tubular dysfunction at an early stage, electrophoretic examination of urine proteins or determination of certain low molecular weight proteins must be used. Once fully established, the renal dysfunction does not regress, even if exposure ceases. The progress is, however, very slow. There is no specific therapy for chronic cadmium poisoning, but treatment can be instituted against the metabolic disturbances.

The extensive literature on toxicological and environmental aspects of cadmium has recently been reviewed in detail by Friberg et al. (1974, 1975) and Fulkerson et al. (1973) and the following review is to a large extent based on those previous reviews.

2. Physical and chemical properties

Cadmium, Cd, atomic weight 112.4; atomic number 48; density 8.6; melting point 320.9°C; boiling point 765°C; crystalline form hexagonal, silver-white malleable metal; oxidation state 2. Some compounds which can be mentioned are cadmium acetate, cadmium sulfide, cadmium sulfoselenide, cadmium stearate, cadmium oxide, cadmium carbonate, cadmium sulfate and cadmium chloride. Of the many inorganic cadmium compounds, several are quite soluble in water, e.g. the acetate, chloride and sulfate. Cadmium oxide is insoluble in water, whereas cadmium sulfide is almost insoluble. Cadmium is easily complexed with some organic compounds, e.g. thiocarbamates, this property furnishing the basis for several analytical methods. There are some synthetic organometallic compounds, but these have not been found in the general environment, since they are rapidly decomposed

3. Methods and problems of analysis

Dithizone methods have long been used extensively for the analysis of cadmium and amounts of about 100 ng may be determined accurately (Smith et al., 1955). Emission spectroscopy has earlier displayed varying sensitivity and accuracy for cadmium. Modern equipment seems to ensure accurate analysis of about 50 ng (Imbus et al., 1963).

Neutron activation analysis is regarded as an accurate method, but has not been widely used for cadmium (Westermark and Sjöstrand, 1960; Linnman et al., 1973). In vivo determination of cadmium in liver by neutron activation has been described by Harvey et al. (1975). In cadmium exposed workers it was possible to demonstrate elevated liver levels of cadmium. A further development of this method has brought about portable equipment for field use (Thomas et al., 1976).

The usefulness of newly developed electrochemical methods, such as anodic stripping voltammetry, for determination of cadmium in biological material is difficult to evaluate at present.

Atomic absorption spectrophotometry is the most common method for the determination of cadmium to date. By flameless AAS methods, about 5 µg/kg can be accurately determined. However, interference of salts (e.g. Na-salts), may cause inaccuracies if appropriate precautions are not taken (Pulido et al. 1966; Kjellström et al. 1974).

In the past and even into the present, a substantial amount of published data has been based on inadequate methods. Errors have been seen with regard to both emission spectroscopy and atomic absorption spectrophotometry (Fulkerson et al., 1973; Friberg et al., 1974).

4. Production and uses

4.1 Production

Cadmium displays chemical similarity to zinc and occurs together with zinc, the cadmium: zinc ratio in minerals and soils being 1:100-1:1000. Cadmium is obtained as a by-product in the refining of zinc and other metals, particularly copper and lead. There is no specific cadmium ore worth mining for its content of cadmium only. The world production of the metal in 1970 was 16,000 tons. It had increased yearly with 14 % during the preceding five years. Only a very minor part of this world production is recycled, and cadmium has been named "the dissipated element" (Fulkerson et al., 1973).

Although cadmium has been recognised for only a relatively short period of time, environmental pollution has taken place for several thousand years, ever since man started to produce metals from ores which happened to contain cadmium.

4.2 Uses

Cadmium is used in a number of industrial processes. Because of its ability to protect iron items from rusting, it is used for coating such items by electroplating. Cadmium-plated parts for automobiles and the like are more resistant to rust than zinc-coated (galvanized) objects. Cadmium sulfide and cadmium sulfoselenide are used as color pigments in plastics and in various types of paint. Cadmium stearate is used as a stabiliser in plastics. Because of its ability to stiffen copper and increase its mechanical resistance at increased temperatures, it is used in copper-cadmium alloys, which are used for automobile radiators and the like. Cadmium may serve as an electrode component in so-called NIFE alkaline accumulators (Fulkerson et al., 1973). Cadmium is also used in silver solders. During a recent year in the U.S.A. 60 %

of the cadmium produced or imported was used for plating, 11 % in color pigments, 19 % as stabilizers in plastics, 3 % in accumulators and 7 % for other purposes (U.S. Environmental Protection Agency, 1975). In U.K. and West Germany about one third of annually produced or imported cadmium was used for plating and one third as pigments and stabilizers (Teworte, 1973).

5. Environmental levels and exposures

5.1 General environment

5.1.1 Food and daily intake

An extremely wide range of cadmium concentrations in foodstuffs has been reported from various countries. Different results from different investigators analysing the same types of food in the same area can be explained in some cases by the inadequate analytical methods.

When data from reliable analyses performed in several countries are considered (Schroeder and Balassa, 1961; Essing et al., 1969; Rautu and Sporn, 1970; Ministry of Agriculture, Fisheries and Food (UK), 1973; Beckman et al., 1975; Mahaffey et al., 1975; Kjellström et al., 1975; Jönsson, 1976), the following concentrations (mean values mg/kg wet weight) emerge:

Beef meat	0.03 - 0.06
Beef kidney	0.2 - 1.6
Fish meat (other than crab)	0.01 - 0.2
Wheat grains	0.01 - 0.15
Rice (USA & Hungary)	0.03 - 0.04
Rice (Japan, non-contaminated areas)	0.05 - 0.07
White bread	0.02 - 0.16
Milk	<0.001
Potatoes	0.001 - 0.09

These values have been obtained in areas generally believed to be non-contaminated by cadmium. In some contaminated areas of Japan average concentrations of about 1 mg Cd/kg have been found in rice and considerable increases in certain marine products have been found as well.

Estimations of the daily intake of cadmium based on data on cadmium concentrations in single foods and on total diet studies have been made in several countries. In "uncontaminated" areas the average daily intake ranges from 25 to 60 µg/day for a 70 kg person (Friberg et al., 1974). An extensive study from U.K. recently estimated the intake at between 10 and 30 µg for a 70 kg person (Ministry of Agriculture, Fisheries and Food, 1973). Recent estimates from Sweden indicate that the daily intake there is 10-20 µg (Wester, 1974; Elinder et al., 1976). In U.S.A. yearly estimates 1968-1974 for 15-20 year old males (the period of highest calorie intake) have varied between 26 and 61 µg, on an average 39 µg (Mahaffey et al., 1975).

Measurement of cadmium in the feces will give an approximate estimate of the daily intake since 90-95 % of ingested cadmium will remain unabsorbed. Studies performed on this material agree with the range estimated above for daily intake of cadmium (Friberg et al., 1974, 1975; Wester, 1974).

5.1.2 Water and soil

In natural water cadmium is found mainly in bottom sediments and suspended particles, whereas the concentration in the water phase is low. Cadmium concentrations in non-polluted natural waters usually are lower than 1 µg/l. Contamination of drinking water may occur as a result of cadmium impurities in the zinc in galvanized pipes, and the presence of cadmium-containing solders in fittings, water heaters, water coolers and taps.

Concentrations up to 16 mg/kg have been reported in soft drinks which had been in contact with cadmium-containing parts in vending machines. Regular drinking water usually does not have concentrations of cadmium exceeding 5 µg/l. Seawater contains between 0,04-0.3 µg/l.

Both waterborne and airborne cadmium can cause an increased concentration of cadmium in soil. In non-polluted areas the cadmium concentrations in soil will usually be less than 1 mg/kg. In certain areas of Japan where cadmium pollution has been suspected, levels of between 1 and 69 mg/kg have been found in the top soil of ricefields. The cadmium connected with the epidemic of Itai-itai disease (see below) came from ricefield soil contaminated by cadmium-polluted irrigating water. The use of cadmium-containing sewage sludge and superphosphate as fertilizers in agriculture may also contaminate the soil. Sewage sludge may contain 100 mg cadmium/kg dry weight (Berrow and Webber, 1972). Information concerning the factors determining the uptake of cadmium in plants is scarce, but it has been shown that pH and concentrations of other minerals will be of importance (Linnman et al., 1973). Both rice and wheat can take up considerable quantities of cadmium from soil.

5.1.3 Ambient air

Cadmium in ambient air occurs in particulate form. Its exact chemical form has seldom been reported but it is probable that cadmium oxide is an important part.

Annual averages during 1969 in larger cities of the USA ranged from 0.006 $\mu g/m^3$ - 0.036 $\mu g/m^3$ (National Air Sampling Network, USA). In European countries, urban values of 0.002 - 0.05 $\mu g/m^3$ have been reported. In Tokyo mean values over several months varied from 0.01 - 0.053 $\mu g/m^3$. In nonurban areas lower values were found, 0.001 - 0.003 $\mu g/m^3$. Higher values, weekly means of 0.2 - 0.6 $\mu g/m^3$, have been recorded around certain cadmium-emitting industries (Friberg et al., 1974). Cadmium in air can also be measured indirectly by analysing the cadmium content in mosses or leaves (Rühling and Tyler, 1973).

5.1.4 Tobacco

Smoking of tobacco may be an important route of exposure for the general population. The smoking of one cigarette, generally containing 1-2 μg of cadmium, causes the inhalation of about 0.1-0.2 μg of the metal. A smoker of 2 packs per day may accumulate an additional body burden of about 15 mg cadmium over a 20 year period (Lewis et al., 1972).

5.2 Working environment

Data on cadmium exposure within industries are scarce. Acute inhalation exposures are known to occur in e.g. welders of cadmium-containing materials. Systematic studies in the breathing zones of workers in industries where prolonged exposures take place are not known. Sporadic measurements in some industries producing alkaline batteries in the 1940's and 1950's indicate that exposure to cadmium oxide dust, particle size not known, reached a couple of mg/m^3 of air (Friberg, 1950). Later studies in the same type of industry indicate that concentrations have been generally lower, in the range of 50-200 μg/m^3 (Friberg et al., 1974). In the manufacturing of cadmium alloys the exposure is mainly to cadmium fume which consists of cadmium and cadmium oxide particles, generally of smaller aerodynamic diameter than cadmium oxide dust. Concentrations of cadmium in the air of such industries have ranged from 4-270 μg/m^3.

The magnitude of exposure to cadmium in the plating industry has not been reported but it is conceivable that both inhalatory and transdermal exposure could occur. The production and use of cadmium pigments may give rise to inhalation of high concentrations of cadmium oxide, carbonate, sulfide and sulfoselenide in air.

6. Metabolism

Data on absorption, retention, distribution and excretion of cadmium are fundamental for the evaluation of the risks to human health connected with exposure to cadmium. Though an abundance of such data is available, several gaps in the knowledge at hand continue to hamper an exact evaluation.

6.1 Absorption

6.1.1 Inhalation

Cadmium exposure via inhalation is in the form of an aerosol. General laws governing deposition of particulate matter in the lung indicate that, depending on particle size, between 10-50% of the inhaled particles will be deposited in the alveolar part of the lung. For the finely dispersed cadmium aerosols, as is the case due to exposure via cigarette smoking, it can be calculated, based on cadmium concentration in cigarette smoke and autopsy data from people smoking different quantities of cigarettes, that absorption is between 25 and 50% (Lewis et al., 1972; Friberg et al., 1974; Elinder et al., 1976). There are no industrial data which lend themselves to an exact calculation of absorption of inhaled cadmium. Animal data, both from single and chronic exposure studies, indicate a high absorption of cadmium via the respiratory route, between 10 and 40% of the cadmium inhaled. Particles of larger size and particles with very low solubility will probably be in the lower part of this range, while particles with high solubility and smaller diameter will be in the upper part (Friberg et al., 1974).

6.1.2 Ingestion

Absorption of cadmium through food is most important for the non-industrially exposed. In several reports in which the fate of a single oral dose of radioactive cadmium has been followed in rats, mice and monkeys, an absorption of between 0.5-3% has been found (Friberg et al., 1974). The absorption in humans is higher. Five volunteers given a single dose of radioactive cadmium by mouth showed an average absorption of 6% (Rahola et al., 1972) with a range between 4.7-7.0 %. Animal experiments have shown that a low intake of calcium, iron and protein may increase the absorption considerably. It is likely that the situation for the human being is similar, which may be of importance above all in certain highly exposed areas in Japan.

6.2 Transport and distribution

After absorption from the lungs or the gut, cadmium is transported via the blood to other parts of the body, and stored mainly in liver and kidneys. Upon chronic exposure in animal experiments, about 75 % of cadmium injected or absorbed from the gut is found in these two organs. In normal humans, after long-term low level exposure, about 50 % of the retained cadmium is found in the liver and kidneys together and about 1/3 of the body burden is in the kidneys alone. When exposure is excessive, as can be seen industrially and in several contaminated areas in Japan, concentrations of cadmium in liver and kidney are very high as can be seen in Figures 1 and 2. When kidney damage has occurred, cadmium excretion increases considerably, which explains the fact that in the most severely poisoned workers and in Itai-itai patients kidney levels, in contrast to liver levels, are low, often not higher than in normal human beings (Friberg et al., 1974).

A considerable accumulation of cadmium also takes place in pancreas and the salivary glands. In bone tissue, muscles and central nervous system, only small quantities of cadmium are normally found. The placental barrier is effective against penetration of cadmium into the fetus. In the kidney, the highest concentration of cadmium is in the cortex (Friberg et al., 1974).

In the blood of cadmium-exposed experimental animals, cadmium is mainly found in the red cells, where it is bound to a protein of low molecular weight, probably metallothionein. In organs such as kidney, liver, pancreas and testicles, cadmium is also bound to a great extent to metallothionein (Nordberg, 1972; Nordberg and Nordberg, 1973). This protein has a molecular weight of about 6,000-7,000. It can bind up to 11% of cadmium and zinc, because it has a large number of sulfhydryl (SH) groups. This protein has been isolated in large quantities from the liver of cadmium exposed animals, and similar proteins have also been found in the mucosa of the duodenum of such animals. It is possible that the transport from the gut takes place as a cadmium-metallothionein complex. The low molecular weight of metallothionein enables the protein to be filtered through the glomerular membrane and thereafter reabsorbed from the tubular fluid into the cells of the renal tubules. This mechanism may explain the selective accumulation of cadmium in the kidney cortex (Friberg et al., 1974). It has recently been shown that injected metallothionein is rapidly excreted and accumulates in the kidney (Nordberg and Nordberg, 1975).

6.3 Excretion

As is obvious from what has been mentioned above only a small part of the absorbed cadmium will be excreted. This excretion takes place via feces and urine, and comprises probably only 0.005-0.01 % of the total body burden of cadmium in human beings. The excretion via urine increases with age on a group basis and is proportional to the body burden of cadmium. This has been possible to show in animal studies (Nordberg, 1972) and is supported by findings in studies on human beings (Tsuchiya et al., 1972). The individual variation is large as can be seen from Figure 3.

When renal damage has occurred, the cadmium excretion by urine increases dramatically, as shown in studies on rabbits and mice (Friberg, 1952; Nordberg, 1972; Friberg et al., 1974).

6.4 Biological half-time

Once absorbed, cadmium is very efficiently retained in the body, and very small quantities are excreted. The biological half-time in the mouse and in the rat is 200-400 days regardless of the exposure route. In squirrel monkeys it is probably around 2 years (Nordberg,1972). The biological half-time in the human kidney is very long, probably between 20-40 years. In long-term low level exposure, such as arises from natural levels of cadmium in the environment, accumulation in the kidney thus will take place during the whole life-span. This is in accord with observations on the cadmium content in organs from human beings (Figures 1 and 2).

6.5 Mathematical model for cadmium accumulation in renal cortex

Of the total body burden in a normal human being, about 1/3 will be in the kidneys, with the concentration in the kidney cortex being 1.5 times that in the whole kidney. By using equations for accumulation, the concentration in the kidney cortex can be calculated. Kidney weight and caloric intake vary with age, which influences the shape of the curves when the kidney cortex concentration in various age groups is to be calculated. Taking these matters into consideration, theoretical accumulation curves can be calculated with empirically obtained values. If theoretical accumulation curves (Friberg et al., 1974) are compared with empirical values (Figure 4), it is obvious that the excretion constant is somewhere between 0.00005 - 0.0001, corresponding to a biological half-time of 19-38 years.

7. Levels in tissues and biological fluids, normally and as indices of exposure and concentrations in critical organs

Newborn babies are almost free of cadmium, the total body burden being only about 1 μg (Henke et al., 1970). A man of 50 years of age in USA, Sweden and East Germany will have a total body burden of cadmium of between 15-30 mg. This corresponds to concentrations in the liver of about 2-3 mg/kg wet weight and in the kidney cortex, 25-50 mg/kg (corresponding to about 15-20 mg/kg calculated on a whole kidney).

Normal values in Japan are higher, e.g. data from Tokyo indicate average kidney cortex concentrations at age 50 of above 100 mg/kg (Friberg et al., 1974; Tsuchiya et al., 1972).

The variation of "normal" levels in liver and kidney cortex according to age and area is shown in Figures 1 and 2. There will also be differences between smokers and nonsmokers.

In blood "normal" levels in nonsmokers are generally below 1 μg/l, whereas considerably higher values, up to 7.6 μg/l, have been found in smokers (Ulander and Axelsson, 1972). There are great discrepancies among published data on "normal" blood levels but it has been concluded that most data speak in favor of the low levels presented above (Friberg et al., 1974, 1975).

In urine "normal" levels will also vary with age, area, and smoking habits, generally being <1 μg/g creatinine, but 1-2 μg/g creatinine has been reported in some areas in Japan (Friberg et al., 1974, 1975).

7.1 Concentrations in biological material as indices of exposure

Available evidence from animal experiments and human data have been compiled (Friberg et al., 1974), revealing that during exposure blood values probably do not reflect kidney accumulation of cadmium, but may reflect the most recent exposure.

Whereas it may thus be difficult to use blood values for an evaluation of renal cadmium concentrations, blood values might be possible to use for evaluations of exposure. Experience is not yet sufficient to state a numerical relationship between blood concentration and exposure.

It has been shown (Nordberg, 1972) in animal experiments that during the early phase of exposure, before renal tubular impairment has occurred, a correlation exists on a group basis between the body burden and urinary concentration of cadmium. Tsuchiya et al. (1972), in studies on normal Japanese not excessively exposed to cadmium, found that on group basis the urinary concentrations of cadmium followed the accumulation of cadmium in the kidneys as seen in autopsy cases. A large individual scatter was evident, however (Figure 3).

7.2 Concentrations in biological materials as indices of concentrations in critical organ

Conclusive evidence on the relation of blood values of cadmium to the concentration in the kidneys has not been presented.

The biological half-time in the blood seems to be shorter than in the kidney. This means that high blood values may be found before critical levels are reached in the kidneys while low blood values do not exclude the possibility that a considerable cadmium accumulation has taken place in the body.

Based on animal as well as human data it seems that cadmium in urine theoretically could be used as an index of the body burden and the concentrations in the kidneys. In long-term, low level exposure, a urinary cadmium excretion of about 10 mg/kg creatinine indicates that in the renal cortex the cadmium concentration is near the critical concentration (Piscator, 1972). At high exposures the excretion of cadmium may be quite high, reflecting more recent exposure. Further, as has been referred to earlier, when tubular dysfunction occurs an increase of urinary excretion of cadmium will occur. When excretion of cadmium in urine is excessive suspicions will always exist that tubular dysfunction has already arisen.

8. Effects and dose-response relationships

Cadmium may give rise to both acute and chronic types of poisoning. The following review will describe symptoms and signs in human beings suffering from such poisoning, but will also deal with animal data that may have a bearing on the interpretation of these effects both clinically and from the standpoint of establishing adequate dose-response relationships for setting of standards.

8.1 Acute poisoning

8.1.1 Inhalation

The symptoms may not appear until 24 hours after exposure has terminated, which may cause difficulties in obtaining the proper diagnosis (Friberg et al., 1974). The predominant symptoms and signs are shortness of breath, general weakness, fever and in severe cases respiratory insufficiency with shock and death. The cadmium induced acute pulmonary disorder is a chemical pneumonitis or sometimes a pulmonary edema.

This type of effect may most frequently result from the inhalation of fumes generated by welding upon cadmium-containing materials or by smelting or soldering such materials, both under conditions of poor ventilation. Approximately 5 mg/m^3 inhaled over a time period of 8 hours may be lethal and approximately 1 mg/m^3 inhaled over the same time period gives rise to clinically evident symptoms in sensitive individuals (Friberg et al., 1974).

8.1.2 Ingestion

The symptoms and signs are nausea, vomiting, abdominal cramps, and headache. In more severe cases diarrhea and shock may develop. The onset of symptoms is usually a matter of minutes upon ingestion of the cadmium-containing food item.

This type of poisoning may arise as a result of contamination of food or drink with cadmium from solders in water pipes, taps, cooling or heating devices or from dissolution of cadmium from pottery, usually when storing acid juices and the like in these items. Cadmium-plated cooking utensils, long since prohibited in most countries, at one time frequently caused acute cadmium poisoning. The concentration of cadmium in water that gives rise to vomiting is about 15 mg/l. For protein containing-foods somewhat larger concentrations are probably required to induce vomiting.

8.1.3 Injection

Injection of single doses of soluble cadmium salts (1-3 mg/kg body weight) gives rise to dramatic effects on the testicles of several species of experimental animals. Effects on non-ovulating ovaries of females as well as on sensory ganglia have also been reported. Within hours after injection, these organs undergo complete destruction, without evident damage to other organs (Parizek, 1956; Gabbiani, 1966; Friberg et al., 1974). A vast literature on various aspects of these effects has been published, but it is of limited value for an evaluation of human health effects from environmental cadmium exposure.

8.2 Chronic poisoning

8.2.1 General aspects

8.2.1.1 Long-term inhalation in industry

Fully developed industrial cadmium intoxication after chronic exposure via inhalation consists of a syndrome including lung emphysema and kidney disease with proteinuria (Friberg, 1950). The relative severity of the renal versus the lung damage is dependent on the intensity of the exposure (and presumably also on variations in individual susceptibility) so that with more intense exposure relatively more lung damage is seen whereas with low exposures for very long time periods, a more or less isolated renal affection may develop.

In addition, anemia, liver disturbance and changes in bone mineral metabolism may be seen.

The concentrations that may give rise to effects will be dealt with more in detail in the section on dose-response relationships (section 9).

8.2.1.2 Long-term ingestion

Long-term ingestion of cadmium has taken place in Japan. It has given rise to a renal tubular disease of the same type as in industrial long-term exposure and as well as a severe bone disease known as Itai-itai disease. The patients may also have gastrointestinal changes with resorption defects, anemia and liver disturbance. For more details on the Itai-itai disease, see sections 8.2.2 and 8.3.6.

8.2.2 Kidney damage

The most typical feature of chronic cadmium intoxication is the kidney damage. Cadmium affects reabsorption functions of the proximal tubules and the first sign is usually an increase in the excretion of low molecular weight proteins - tubular proteinuria (Figure 5). Normally, these proteins occur in plasma, are filtered through the glomeruli, and are reabsorbed almost completely. One of these proteins is β_2-microglobulin. The cadmium poisoned kidney reabsorbs these proteins to a lesser extent which results in an increase in protein excretion. Later effects may be aminoaciduria, glucosuria and phosphaturia (Piscator, 1966). Disturbances in the renal handling of phosphorus and calcium may cause resorption of minerals from bone. Signs of these disturbances have been kidney stones in Swedish workers (Friberg, 1950; Axelsson, 1963), and osteomalacia in French workers (Nicaud et al., 1942).

Tubular dysfunction of the same type as seen in cadmium workers has been a common finding in cadmium-contaminated areas in Japan, especially in Fuchu, Toyama Prefecture, where the so-called Itai-itai disease was first seen. This disease is an osteomalacia, which mainly has been found in women above 45 years of age and with many pregnancies. Low calcium intakes and losses of calcium during pregnancy and lactation periods contribute to this extreme manifestation of chronic cadmium poisoning.

Once tubular proteinuria is manifest, it persists even if exposure ceases, as has been shown by long-term observations on cadmium workers (Piscator, 1966). It is not known whether or not the very first changes in reabsorption are reversible.

8.2.3 Anemia

Slight decreases in hemoglobin levels have been a common finding in cadmium exposed workers. This is a reversible effect and bears no relationship to the renal damage. Cadmium probably has no direct effect on hematopoiesis, but the deficient iron absorption from food engenders decreased availability of iron to the bone marrow. Decreased haptoglobin levels have also been observed in cadmium workers and in animal experiments indicating that the anemia may be partly of hemolytic origin. An increased destruction of erythrocytes has been shown in animal experiments (Friberg et al., 1974).

8.2.4 Hypertension

Some animal experiments show that hypertension can be induced by cadmium (Schroeder, 1964). This is not always the case, as indicated by later authors. Both differences in susceptibility among strains and in intake of sodium have been implicated as important factors (Friberg et al., 1974).

Autopsy studies pointing towards a higher concentration of cadmium in people dying of cardiovascular diseases have been reported (Schroeder, 1967). The effect of smoking was not taken into account. There are no reports of hypertension in industrially exposed workers, but the question has not been carefully evaluated. Whether cadmium actually affects the blood pressure in human beings cannot be said at present.

8.2.5 Liver disturbances

The liver is one of the major storage organs for cadmium and may be adversely affected by this metal. In exposed workers changes in liver function generally are slight compared to the changes in renal function. Data from animal experiments (Friberg, 1950; Sporn et al., 1970; Stowe et al., 1972) indicate that morphologically evident damage as well as changes in the activity of certain enzymes in the liver may occur at long-term parenteral or oral exposures. Such changes may occur without showing up on classical clinical diagnostic tests for liver damage.

8.2.6 Effects on bone

As mentioned in 8.2.2, the renal damage disturbs the metabolism of bone minerals. Some experimental data suggest that cadmium may also affect calcium metabolism before renal damage has occurred. In calcium-deficient animals the retention of cadmium was higher than in animals on a normal calcium intake and cadmium accelerated the osteoporotic process caused by calcium-deficiency alone (Larsson and Piscator, 1971; Piscator and Larsson, 1972). High oral exposure has also caused osteomalacia in animals at renal cortex concentrations of cadmium of only about 50 mg/kg wet weight (Kawai et al., 1976).

The Itai-itai disease is an osteomalacia caused by the combination of primary calcium deficiency and severe tubular dysfunction from cadmium exposure. The symptoms are dominated by pains in the back and legs. Pressure on bones, especially the long bones in the legs and the ribs, produces further pain. When the disease progresses, even mild trauma may give rise to fractures of various parts of the skeleton. Skeletal deformation takes place with a marked decrease in body height (Tsuchiya, 1969; Friberg et al., 1974).

8.3 Carcinogenic effects

In human beings interest has mainly been focused on cancer of the prostate, since Potts reported in 1965 that 8 deaths had occurred among 74 men with at least 10 years of exposure to cadmium oxide dust and that 3 of them were from cancer of the prostate. Kipling and Waterhouse (1967) found that 4 deaths from cancer of the prostate had occurred in 248 workers from the same factory (including those described by Potts, 1965) with more than 1 year of exposure. The expected number was 0.58. Lemen et al. (1976) reported that 4 of 292 smelter workers with at least 2 years of exposure to cadmium oxide dust and fumes had died from cancer of the prostate, whereas the expected number was 1.15. When the time elapsed since the onset of exposure was taken into account, a significantly increased risk of cancer of the prostate was shown, 4 observed as compared to 0.89 expected, 20 years after the onset of exposure. The numbers in these two studies are low and the data are not yet conclusive.

Cadmium sulfate given subcutaneously to rats and mice repeatedly over a two-year period did not lead to any signs of malignant tumors in the prostate (Levy et al., 1973).

With regard to other forms of cancer Lemen et al. (1976) reported a significant excess of respiratory cancer, 12 deaths versus 5.11 expected in the above mentioned group of smelter workers. Data on smoking were not given, however.

Among the 58 Swedish battery workers reported on by Friberg (1950) 17 had died in 1972, 3 of them in cancer of the urinary bladder, lung and large bowel respectively (Friberg et al., 1974). There was no control group, and no conclusions can be drawn.

The association between occupational cadmium exposure and cancer has been evaluated by IARC (1976). It was stated, "Available studies indicate that occupational exposure to cadmium in some form (possibly the oxide) increases the risk of prostate cancer in man. In addition, one of these studies suggests an increased risk of respiratory tract cancer."

Intensified studies on groups of humans exposed occupationally or through food are fully motivated by the data at hand.

8.4 Genetic effects

Data on genetic effects are scarce. One study on Itai-itai patients did show some chromosome aberrations (Shiraishi et al., 1972) while another one did not show any such effects (Bui et al., 1975). In exposed workers, Bui et al. (1975) did not find any chromosome anomalies, whereas Deknudt and Leonard (1975) found a significant increase in anomalies. In mice examined 3 months after a single interperitoneal injection of 1.75 mg Cd/kg, no chromosome abnormalities were found (Gilliavod and Leonard, 1975).

Doyle et al. (1974) exposed lambs to cadmium via feed (60 µg Cd/kg) for 191 days. They found a significant increase in extreme hypodiploidy, but did not look for chromosome aberrations. Available data thus do not show any consistent pattern but clearly indicate a need for further research.

8.5 Teratogenic effects

In animal experiments teratogenic effects have been shown after single injections of high doses (3 mg Cd/kg or more) to pregnant golden hamsters or rats. Effects include cleft lips and palates and limb defects (Ferm and Carpenter, 1968; Friberg et al., 1975). Schroeder and Mitchener (1971) found teratogenic effects after long-term exposure to 10 mg cadmium/l in double deionized water. The mice were followed for three generations and congenital abnormalities, including sharp angulation of the distal third of the tail, were observed in several litters. Such effects may be caused by zinc deficiency due to the retention of zinc in the mothers (Friberg et al., 1974).

No reports on teratogenic effects in cadmium-exposed humans have come to the fore. In a study on cadmium-exposed women in the U.S.S.R., malformations were not seen in the newborns but birth weights were lower than in newborns of controls and a few cases of rachitis were seen (Cvetkova, 1970).

8.6 Interaction between cadmium and other metals; biochemical observations

Animal experiments have shown that some effects of cadmium may be prevented by the simultaneous administration of other metals. For example, cadmium-induced acute testicular necrosis can be prevented by administration of zinc, cobalt or selenium. Hypertension elicited by cadmium in rats may be reversed by administration of zinc chelates. Cd-Zn interactions are thought to be of special importance in cadmium toxicity. A biochemical explanation is offered by the replacement of zinc by cadmium in zinc-dependent enzymes. Cadmium causes a redistribution of zinc, more zinc being stored in liver and kidneys and less in some other organs, which also may affect some essential functions. This behavior of cadmium is believed to play a role for other manifestations of cadmium toxicity in addition to those mentioned above (Friberg et al., 1974, 1975).

A biochemical phenomenon that has been studied in relation to cadmium-induced organ damage is the binding of cadmium and zinc to metallothionein. The role of this low molecular weight protein in transport and distribution has already been alluded to. In addition it seems that the binding of cadmium to this protein is inversely related to the occurrence of acute effects of cadmium, e.g. testicular necrosis (Nordberg, 1972).

Metallothionein thus seems to play a dual role in cadmium toxicity. On the one hand it acts as a detoxification agent against the acute effects of cadmium and as a "normal" storage protein for cadmium but on the other hand it may be involved in the elicitation of the critical chronic effects of cadmium on the kidney (Nordberg et al., 1975).

In normal human beings the increase in cadmium in the renal cortex with age is accompanied by an equimolar increase in zinc. This is thought to be due to the metallothionein stored in the kidney, which contains equimolar amounts of the two metals (Piscator and Lind, 1972).

9. Dose-response relationships

9.1 Based on critical concentration in the kidney and a metabolic model

Information about morphological changes, proteinuria and cadmium levels in kidneys of human beings is available from about 30 autopsies and biopsies from persons exposed to cadmium. It is not possible to establish a detailed dose-response curve with this limited amount of data at hand. In persons with no renal changes or only slight changes in tubular function cadmium levels in kidney cortex with one exception varied between 150 and 450 mg/kg wet weight (Friberg et al., 1974).

Animal data provide much evidence that tubular dysfunction and/or morphological kidney changes occur at kidney cortex concentrations of 200-400 mg/kg wet weight (Bonnell et al., 1960; Axelsson et al., 1968; Stowe et al., 1972; Nomiyama et al., 1976; Kawai et al., 1974). Some data speak in favor of an effect at even lower concentrations (Piscator and Larsson, 1972; Kawai et al., 1976).

Friberg et al. (1974) when evaluating human and animal data, concluded that the critical level in the kidney cortex of the more sensitive part of the population should be about 200 mg/kg. A WHO group has concluded that the critical level may be between 100 and 300 mg/kg, with 200 mg/kg as the most likely estimate (WHO, 1977).

Using a metabolic model and assuming a critical concentration of 200 mg/kg wet weight in kidney cortex, calculations of exposure situations giving rise to this concentration can be worked out and have been presented by Friberg et al. (1974). Data for industrial exposure and exposure via food are given in Tables 1 and 2 respectively. Different assumptions concerning the biological half-time have been used. If the biological half-time is set at 19 years and the pulmonary absorption at 25 %, it can be calculated that a cadmium concentration in inhaled air of 13 µg/m^3 under industrial exposure conditions (ventilation 10 m^3 per day during an 8-hour workday, 225 workdays per year) would give rise to the critical renal cortex values after 25 years of exposure. With a biological half-time of 38 years the corresponding value would be 11 µg/m^3. The necessary daily cadmium intake via food for an adult, caloric intake = 2,500 calories = to reach the critical concentration at age 50 would be 350 µg/day or 250 µg per day under the assumption of a biological half-time of 19 years and 38 years, respectively.

9.2 Based on direct observations of dose and effect

Data from industrial exposure (Bonnell, 1955; Bonnell et al., 1959; Harada, 1973; Harada, 1974; Friberg et al., 1974; Lauwerys et al., 1974; Kjellström et al., 1977) may favor the assumption that 50 µg/m^3 gives rise to up to 50 % prevalence of cadmium induced tubular proteinuria after prolonged exposure. These data are very uncertain.

Increasing prevalence of proteinuria and glucosuria in relation to dose has been reported from Japan. Dose in Japan is often estimated from the cadmium concentration in rice. From the data by Fukushima et al. (1973), it can be estimated that an increase in this concentration from about the one found in non-polluted areas: 0.05 mg Cd/kg (wet weight) to 0.5 mg Cd/kg would increase the prevalence of concurrent proteinuria and glucosuria among people over 50 years of age from about 5 % to about 20 %. This estimation is supported by results obtained by Kjellström et al. (1977).

Comparisons between polluted and control areas show statistically significant differences in prevalence of proteinuria in at least four different areas, but the epidemiological methodology is often not designed for dose-response studies. It has been concluded, however (Friberg et al., 1974, 1975), that somewhere between 0.4 and 0.6 mg Cd/kg in rice the exposure would be so high as to induce tubular proteinuria in a significant part of a population. These figures correspond to a daily intake of about 0.24-0.36 mg. Similar estimates have been made by a WHO expert group which concluded that cadmium concentrations in rice of 0.5-0.8 mg/kg caused an increase in the prevalence of tubular proteinuria, corresponding to a daily intake of 0.30-0.48 mg. An estimate based on the fecal excretion of cadmium showed that about 0.20 mg per day could cause the increase in the prevalence of proteinuria (WHO, 1977).

The figures thus are in fairly good agreement with the figures reached when using the metabolic model for cadmium and starting from a critical kidney cortex concentration of 200 mg/kg wet weight.

10. Diagnosis, prognosis and treatment of cadmium poisoning

10.1 Acute poisoning

10.1.1 Inhalation

10.1.1.1 Diagnosis

Acute cadmium intoxication should be suspected when respiratory symptoms occur suddenly in welders. The welder himself may not be aware of having worked with cadmium-containing material. The diagnosis in such cases rests upon identification of cadmium related exposure. Amounts of cadmium involved are relatively small. It is not certain that blood values will be clearly above normal limits, but confirmation by cadmium analyses of blood should be attempted. Such analyses should preferably be done as soon as possible after exposure and repeated at intervals.

10.1.1.2 Treatment and prognosis

Results from animal experiments (MacFarland, 1960) indicate that treatment with adequate doses of BAL as soon as possible after exposure may be beneficial in acute cadmium poisoning. Such treatment should be given under careful observations of signs of renal complications (including tests for proteinuria, indicating renal tubular damage) since BAL is likely to translocate cadmium from pulmonary to renal tissues. In workers with previous long-term exposure to cadmium, BAL should not be given since renal damage is likely to be precipitated thereby. In addition it is evident that general symptomatic treatment of respiratory insufficiency should be included.

Prognosis after regression of the acute symptoms is usually good but an incapacitating pulmonary disease may remain for years.

10.1.2 Ingestion

This type of acute cadmium poisoning should be suspected whenever the symptoms mentioned in section 8.1.1 arise. What is indicative is the generally very short interval between ingestion of contaminated food or drink and vomiting. Treatment is symptomatic and prognosis usually good when the acute symptoms have subsided. Complications are not known, but no follow-up studies have been reported.

10.2 Chronic poisoning

10.2.1 Diagnosis

10.2.1.1 General aspects

The diagnosis of chronic cadmium poisoning rests on identification of long-term cadmium exposure and symptoms (see section

8). Appropriate spirometric and other investigations should be performed to identify signs of emphysema. Blood chemistry and even bone biopsy may be necessary together with appropriate X-ray investigations for diagnosis of cadmium-related osteomalacia.

10.2.1.2 Tubular proteinuria

Since there are no accurate means of predicting renal burdens of cadmium, it is of utmost importance to use reliable methods to detect early changes in protein excretion, since cessation of exposure at that stage may prevent more extensive damage.

Qualitative tests, using trichloracetic acid or sulfosalicylic acid, are useful for detecting a fully developed proteinuria. Test tapes are not sensitive enough. Quantitative determination of urinary protein is not always sufficient, since the excretion of some low molecular weight proteins might be increased considerably while the total protein is still within the normal range (Piscator, 1972). Electrophoretic separation of concentrated urinary proteins makes it possible to detect small changes in the distribution of proteins, but also has its limitations. Accurate quantitative determination of small increases in the urine of certain low molecular weight proteins, e.g. β_2-microglobulin, is possible and has recently been introduced in the routine control of cadmium workers. This method also has its limitations in that the excretions may vary with the pH of the urine. The general status of the renal handling of proteins is not revealed by this method. A combination of determination of total protein, β_2-microglobulin and electrophoretic separation is probably the best way to obtain an accurate estimate of renal status (Piscator, 1972). In more advanced cases, diagnosis is easily obtained by electrophoretic methods, as shown in Figure 5.

10.2.1.3 Cadmium determinations in blood and urine

As discussed in section 7, there are not any good means of estimating renal cadmium accumulation based on urine or blood concentrations of cadmium. However, such determinations may be helpful in diagnosis. In long-term low level exposure a urinary cadmium concentration above 10 µg/l or 10 mg/kg creatinine generally signals impending or actual renal tubular impairment. A blood value above 10 µg/l tells us that cadmium exposure of a significant degree has taken place. It is not always possible to gauge the risk for renal damage on the basis of the blood values.

10.2.2 Treatment

Some chelating agents like EDTA can cause a redistribution of cadmium in the body so as to increase renal accumulation of cadmium. The use of chelating agents therefore should be warned against, since they might cause the renal dysfunction to undergo further impairment (Friberg, 1956; Friberg et al., 1974).

In cases of manifest tubular damage with disturbances in mineral metabolism, treatment should be directed against the metabolic disturbance, e.g. therapy with phosphates could be tried. In cases of Itai-itai disease, large doses of vitamin D have been administered, bringing about a slow healing of fractures and relief from pain. Of importance in these cases is that the patient has an adequate supply of calcium and phosphate in his diet for restoring lost mineral content of bones. Of general importance both from preventive and therapeutic aspects is an adequate intake of zinc and protein.

10.2.3 Prognosis

The prognosis in patients with a slight or moderate isolated renal tubular disorder without emphysema and without complications such as osteomalacia generally is favorable with regard to survival. However, only a few follow-up studies of people with cadmium intoxication have been reported. Mortality figures for workers with fully developed cadmium intoxication in the 1940's in an alkaline accumulator industry show that emphysema and kidney damage are not at all harmless from the standpoint of survival time (Friberg et al., 1974). These workers had a significant overmortality in relation to expected mortality among Swedish men (Figure 6). The exposure in the 1940's was excessive, however, probably now and then several mg/m^3. Workers examined in the early study and some other workers not so heavily exposed were examined in a follow-up study about 10 years after the original examination. It was then shown that persons in whom proteinuria had been established in the first examination still had this damage, despite their having been removed from cadmium exposure.

__Table 1.__ Cadmium concentration in industrial air ($\mu g/m^3$) necessary for exposed workers to reach the critical concentration (200 mg Cd/kg wet weight) in renal cortex under different absorption, excretion and exposure time alternatives. Ventilation = 10 m^3 during an 8-hour workday, 224 workdays per year (From Friberg et al., 1974).

Pulmonary absorption percent	Exposure time in years	Excretion per day, percent of body burden (corresponding biological half-time in years in parenthesis)				
		0 (∞)	0.002 (95)	0.005 (38)	0.01 (19)	0.02 (9.5)
25	10	21.3	22.1	23.3	25.4	30.0
	25	8.5	9.3	10.6	13.0	18.6
	50	4.3	5.1	6.5	9.3	16.0
50	10	10.7	11.1	11.7	12.7	15.0
	25	4.3	4.7	5.3	6.5	9.3
	50	2.2	2.6	3.3	4.7	8.0

Table 2. Necessary daily cadmium intake from food for an adult (daily calorie intake = 2,500 cal) to reach critical concentration (200 mg/kg wet weight) in renal cortex at age 50 along with the necessary cadmium concentration in a basic foodstuff tr reach these cadmium intakes* (From Friberg et al., 1974).

	Excretion per day, percent of body burden (corresponding biological half-time in years in parenthesis)				
	0 (∞)	0.002 (95)	0.005 (38)	0.01 (19)	0.02 (9.5)
Cadmium intake	164	196	248	352	616
Cadmium concentration in basic foodstuff mg/kg wet weight	0.27	0.33	0.41	0.59	1.03

* Assumptions:
a) 1/2 of the daily cadmium intake from this foodstuff
b) 300 g of this foodstuff ingested daily
c) 5% absorption of ingested cadmium

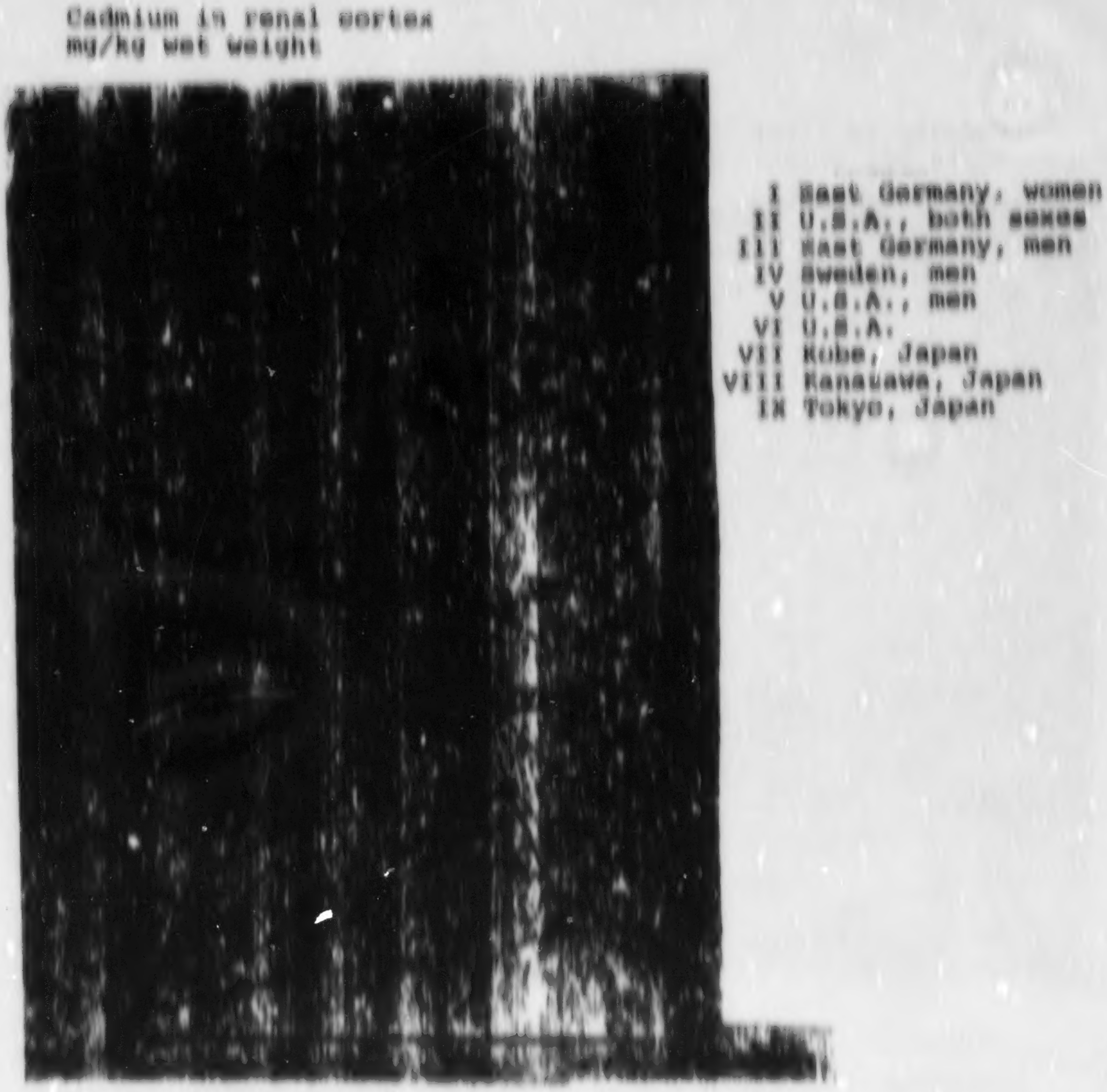

Figure 1.

Cadmium concentrations in renal cortex from normal human beings in different age groups. Linear scale (From Friberg et al., 1974).

Cadmium in liver
mg/kg wet weight

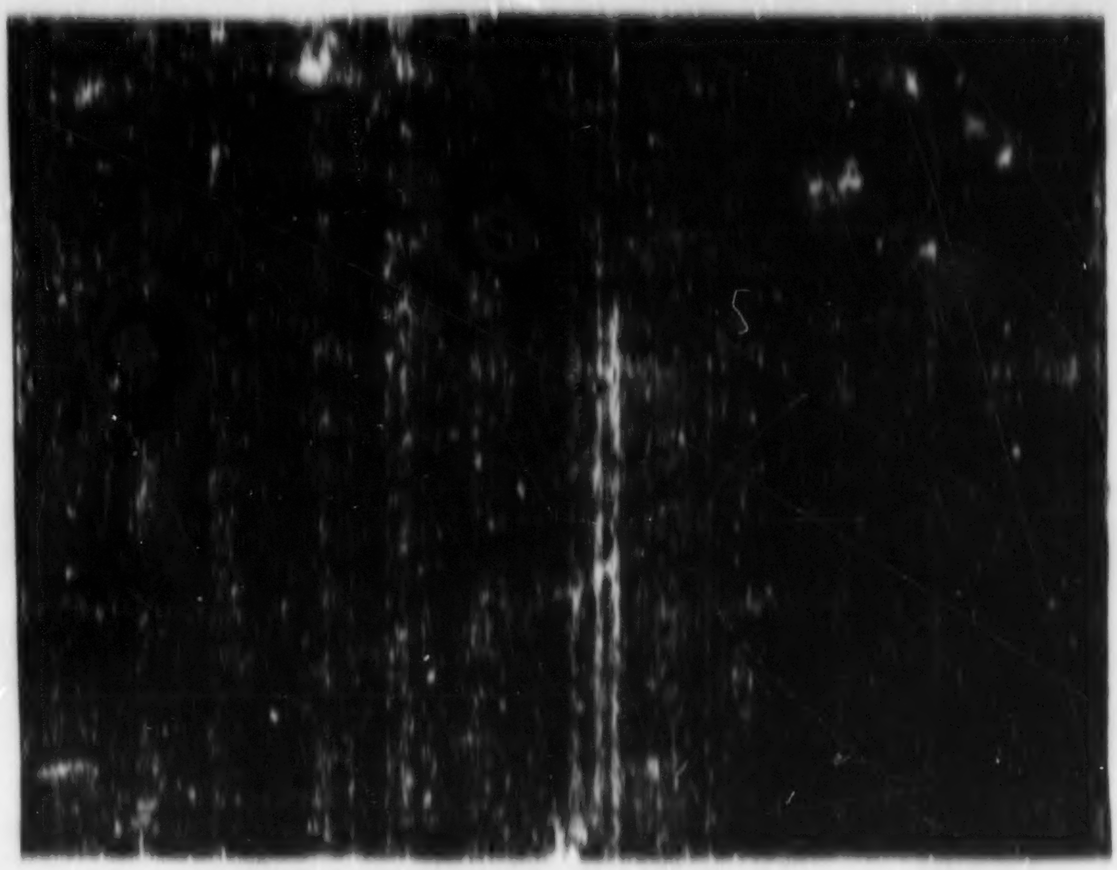

Figure 2.

Cadmium concentrations in liver from normal human beings in different age groups (mean values), exposed workers (single values), and Itai-itai patients (single values) (From Friberg et al., 1974).

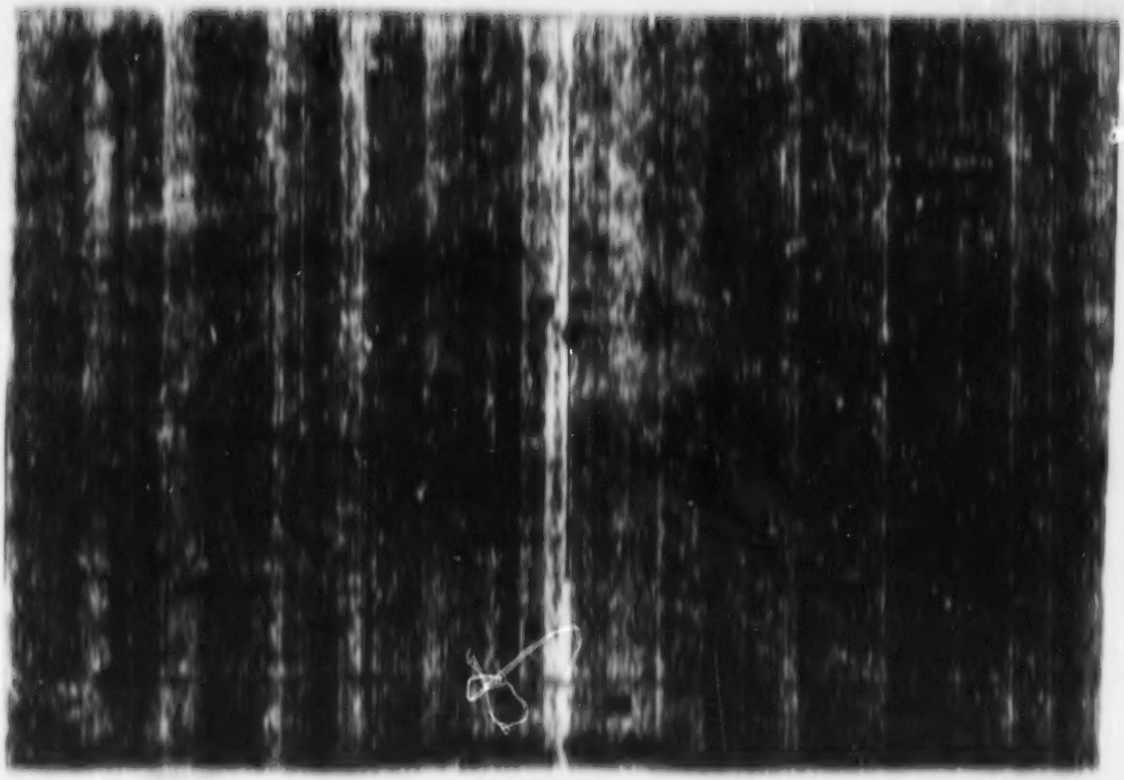

Figure 3.

Average cadmium concentration in urine within different age groups in Tokyo (From Tsuchiya et al., 1972).

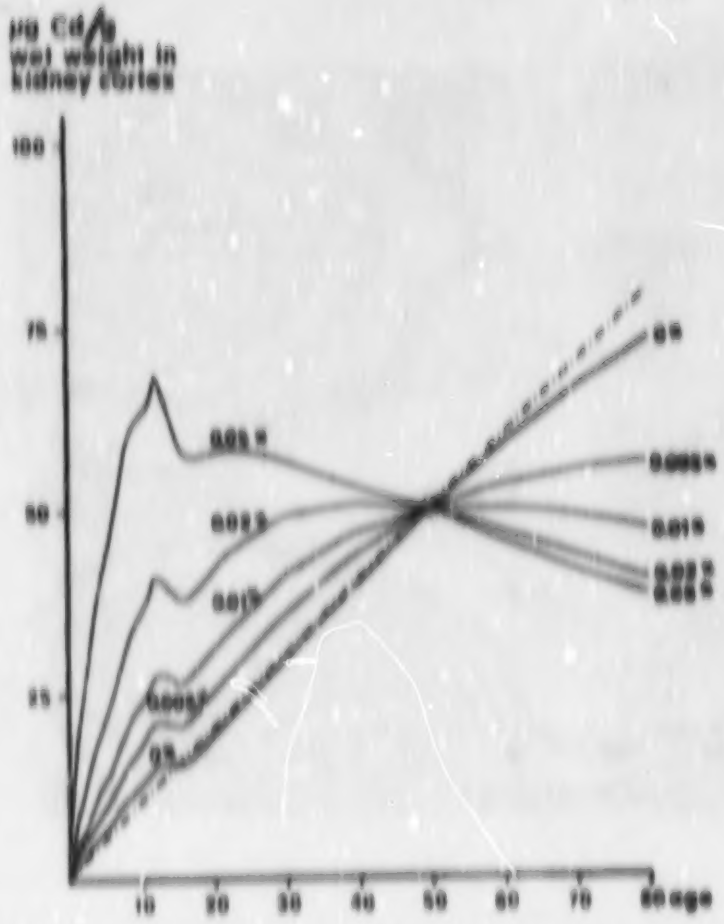

Figure 4.
Calculated cadmium concentrations in kidney cortex by age for different body burden excretion alternatives. Adjusted for variation in calorie intake and kidney weight by age, except dotted line (From Friberg et al., 1974).

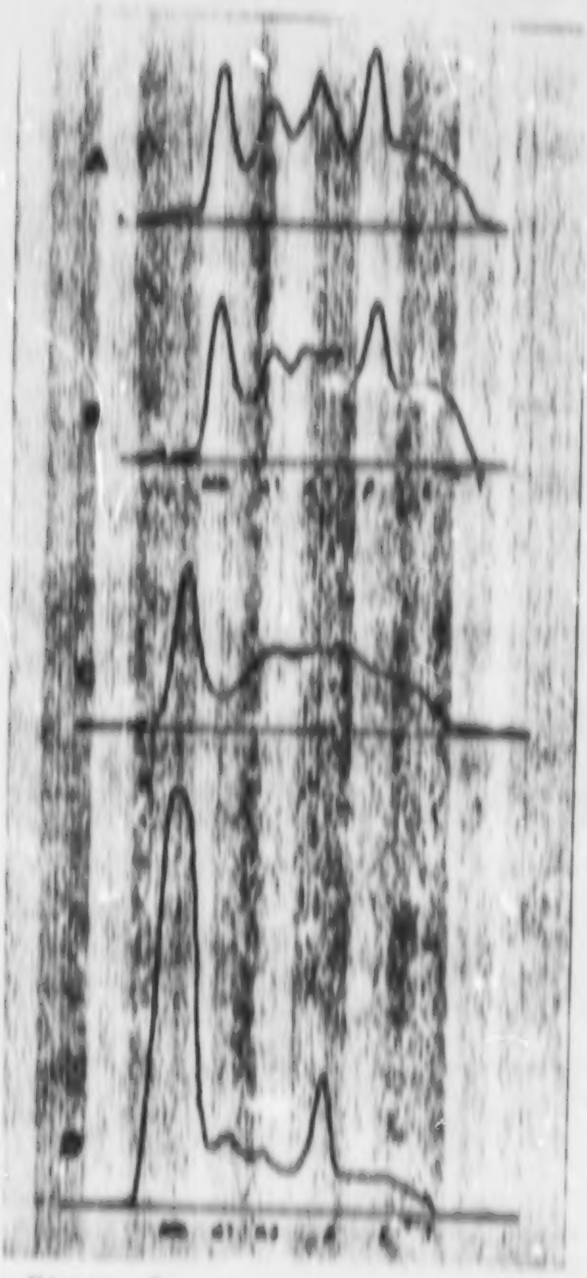

Figure 5.

Scanned electrophoretic patterns for urinary proteins - A and B, Cadmium workers; C, normal man; D, person with chronic nethritis. The prominent β-fraction in A and B is mainly composed of β_2-microglobulin and some other β-proteins, whereas transferrin constitutes only a minor part of the β-fraction (From Piscator, 1966).

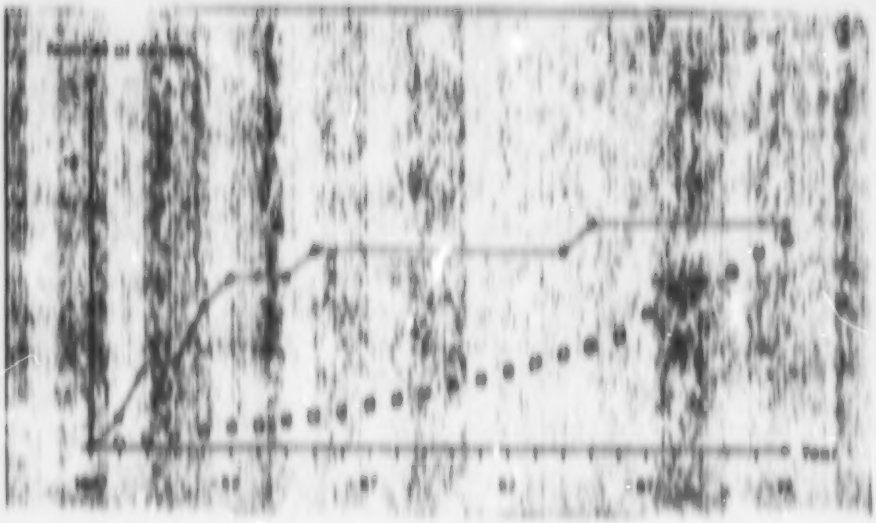

Figure 6.

Observed and expected mortality of 19 Swedish cadmium workers with very high exposure to cadmium at different times after the first clinical investigation in 1947 (From Friberg et al., 1974).

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CHROMIUM

Sverre Langård and Tor Norseth

1. Abstract

In nature most chromium is found in the trivalent state as chromite ore. Dichromate (Cr^{+6}) is produced from chromite ore and the further uses of dichromates and monochromates in the chemical industry are important from an occupational health standpoint.

Chromium in the hexavalent state is more easily absorbed both via lungs and gastrointestinal tract than in the trivalent state. Chromium is found in all organs of the newborn and of adults, the highest concentration in the latter usually being found in lung tissue. An accumulation of chromium with age takes place in the lung as a result of deposition from inhaled air. In all other organs the concentration of chromium decreases with age. Chromium is predominantly excreted in the urine. An exponential character of the excretion with three different half-times of 0.5, 5.9 and 83.4 days has been described in rats.

Chromium is an essential metal in man and in animals and plays an important role in insulin metabolism as the glucose tolerance factor. The daily requirement of chromium in human nutrition has not been established. In man the daily diet is the main source for chromium intake. Small quantities are found in municipal drinking water and in ambient air.

Both acute and chronic adverse effects of chromium are mainly caused by hexavalent compounds which are very toxic to man. There is little conclusive evidence on toxic effects caused by divalent and trivalent chromium compounds. Depending on concentration and exposure time, hexavalent compounds may cause skin ulcerations, irritative dermatitis, allergic skin reactions and allergic asthmatic reactions. Hexavalent chromium may also cause ulcerations in the mucous membranes and perforation of the nasal septum.

Inhalation of hexavalent chromium compounds may cause bronchial carcinomas, lung fibrosis and pneumoconiosis. The ability of hexavalent chromium compounds to induce bronchiogenic cancer in humans is well established. However, animal experiments with chromates have not been able to identify the specific hexavalent compound or compounds of most pronounced activity. Hexavalent chromium compounds have been found to induce adenocarcinomas, but not bronchiogenic carcinomas in the lung of experimental animals. Local sarcomas in muscles and local carcinomas of the skin have also been demonstrated. Hexavalent chromium compounds also seem to be mutagenic.

The largest human exposures in the general population are via food. No adverse effects have been reported from such exposures.

The medical and biological effects of chromium have recently been reviewed (Chromium, 1974; Effects of Chromium in the Canadian Environment, 1976). The occupational exposure to chromic acid has been specifically reviewed (NIOSH, 1973), as have the exposure to hexavalent chromium (NIOSH, 1975) and the carcinogenic effect (IARC, 1973).

2. Physical and chemical properties

Chromium, Cr, atomic weight 52; atomic number 24; density 7.2; melting point 1857±20°C; boiling point 2672°C; crystalline form steel gray, cubic, very hard; oxidation state chiefly 2,3,6.

Besides the naturally occurring ferrous chromite, chromium compounds taken up in this chapter include lead or barium chromate, and sodium or potassium chromate or dichromate, chromium acetate, chromium citrate, chromic chloride, chromic acid mist, zinc chromate, calcium chromate and strontium chromate.

The relatively unstable divalent (chromous) ion is rapidly oxidized to the trivalent (chromic) form. Hexavalent chromium compounds (chromates) are oxidising agents. Reduction of the hexavalent form to the trivalent may be of importance for the toxicity of chromium compounds.

Chromium in biological materials is probably always trivalent. For example, the so-called glucose tolerance factor, which has not been fully identified, is a trivalent chromium complex with niacin (Mertz, 1975). Other chromium complexes which biochemically meet some of the requirements of the glucose tolerance factor have been synthesized. No organic chromium complexes of toxicological importance have been described.

3. Methods and problems of analysis

Several methods are available for the analytical determination of chromium in biological material in the range of interest (10-1000 /ug/l), but it is not possible today to generalize as to the best method. Methods for the analytical determination of chromium have been evaluated by Beyermann (1962a, 1962b) and a review of the literature on chromium analysis has been given in Chromium (1974).

The traditional colorimetric method employing the violet complex of 1,5 diphenylcarbazide is still a valuable method for analysing chromium in urine. The detection limit is 3.5 ng but the method is subject to interference by other ions (Beyermann, 1962a, 1962b).

Flame photometry, X-ray emission spectrography and polarography are less sensitive than the diphenylcarbazide method. Polarographic methods with a detection limit as low as 1 ng have been described, but these are also subject to interference by other ions (Beyermann, 1962a, 1962b). Neutron activation does not at present seem to offer special advantages for chromium analysis in biological materials but has been used for the determination of chromium in urine (Cornelis et al., 1975). A gas liquid chromatographic method with a detection limit of 0.01 ng for chromium has been described, but the practical experience (Sievers et al., 1967) with the method is limited to date. Atomic absorption spectrophotometry with a flameless technique was reported to have a detection limit of 0.0125 /ug (Graffiage et al., 1974).

Separate determination of trivalent and hexavalent chromium is possible by analysing the sample before and after oxidizing the trivalent to the hexavalent form. Only the hexavalent form is determined both by the colorimetric 1,5 diphenylcarbazide method and by atomic absorption methods if organic extraction is used to concentrate the sample (Mertz, 1969). Variables not controlled in ordinary extraction and mineralization procedures are introduced when chromium is bound to organic compounds as in the glucose tolerance factor. Methodological problems have caused some disagreement as to the valence state of chromium in biological materials, but most probably only the trivalent form is present (Mertz, 1969).

4. Production and uses

4.1 Production

The only important chromium ore is chromite, $FeOCr_2O_3$, which is never found in pure form. FeO may be replaced with some MgO, and the mineral also contains silica in varying amounts, as well as small quantities of other compounds. The highest grade of ore contains about 55% chromic oxide. Both trivalent and hexavalent chromium are found in nature, but the trivalent is the more common form.

The world production of chromite in 1971 was about 7 million tons, the USSR (about 2 million tons) and the Republic of South Africa (about 1.8 million tons) being the main producers (Morning, 1971). Ferrochromium is produced by direct reduction of the ore. Chromium metal is produced either electrolytically after chemical treatment of high carbon ferrochromium, or by reduction of chromium compounds.

Sodium chromate and dichromate are produced by roasting chromite ore with soda ash, or with soda ash and lime, followed by chemical treatment for removing impurities. Most other chromium compounds are produced from sodium chromate or dichromate.

4.2 Uses

The principal industrial consumers of chromium are the metallurgical, refractory and chemical industries. The US 1971 figures for consumption by these industries were 66%, 18% and 16%, respectively, of the total consumption (Morning, 1971).

An important consumer of chromium for many years has been the tanning industry. Other uses are in pigment production and application, the graphics industry and industries using chromium alloys or plated materials. Ferrochromium and chromium metal are the most important classes of chromium used in the alloy industry.

5. Environmental levels and exposures

5.1 General environment

5.1.1 Food, total daily intake

The daily intake of chromium from food has been estimated to be in the range of 0.03 to 0.1 mg (Schlettwein-Gsell and Mommsen-Straub, 1973). Since other sources contribute only minor amounts in relation to these values they represent also an estimate of the total daily intake of chromium for the general population. Food items vary considerably in concentration of chromium. Among large sources are meat, vegetables and unrefined sugar, while fish, vegetable oil and fruits contain smaller amounts. Values are reported from non-detectable to about 0.5 mg/kg wet weight for various food items.

The glucose tolerance factor is predominantly found in yeast, liver and meats. Of all forms of chromium, this has the highest biological availability to man.

5.1.2 Water, soil, ambient air and cigarettes

The chromium concentration in rivers and lakes is usually between 1 and 10 µg/l, that in seawater being considerably less, from < 0.1 to about 0.5 µg/l (Chromium, 1974). Municipal drinking water has been reported to contain higher amounts of chromium than river water.

Soil content ranges from trace to 250 mg/kg with occasionally higher values. The average chromium concentration in the earth's crust is 125 mg/kg. Chromium in phosphates used as fertilisers may be an important source of chromium in soil, in water, and in some foods.

Urban air concentrations of chromium have been reported from less than 10 ng/m^3 up to about 50 ng/m^3. Annual mean values for rural stations seldom reached 10 ng/m^3 (Chromium, 1974).

Cigarettes have been reported to contain 390 µg/kg of chromium (Schroeder et al., 1962), but no estimates of the inhaled amount from smoking have been published.

5.2 Working environment

Potentially hazardous exposures are incurred in the production of dichromate, in the use of chromates in the chemical industry, in the stainless steel industry, in the production and use of alloys, in refractory work, and in the chromium plating industry.

In the last mentioned industry, the health hazard is related to the chromium-containing mist. Chromium exposure in welders may constitute a health hazard, both because chromium is an important constituent in stainless and acid stable steel, and because chromate is extensively used in anticorrosive paints (Ruf, 1970; Gylseth et al., 1977).

Chromium levels in industry have been reported to only a limited degree. Mancuso (1951) reported exposure levels up to 1 mg/m^3 of chromium in a chromate plant. Most values were in the range of 0.26 to 0.51 mg/m^3. A five-day, eight-hour mean value of 1.35 mg/m^3 of chromates in air was reported for a sack-filling operation in an old chromate plant by Langård and Norseth (1975); in another, modern plant levels were below 0.1 mg/m^3. Most chromium values recorded by personal sampling during 8 hours in a ferrochromium plant were in the range of 0.02 to 0.05 mg/m^3, but occasional values were up to 0.4 mg/m^3 (Gylseth and Øien, 1975). In a recent review a chromium exposure up to about 5 mg/m^3 in the chromium plating industry was mentioned, but most exposure levels reported were in the range of 0.1 to 0.2 mg/m^3 (NIOSH, 1973).

6. Metabolism

6.1 Absorption

6.1.1 Inhalation

There are very few reports on absorption of chromium compounds after inhalation. The high concentrations of chromium found in lung tissue of humans exposed to chromium indicate that at least part of the chromium is deposited in the pulmonary tissue in an insoluble form. From the fact that hexavalent chromium compounds are more soluble it may be assumed that these compounds are more easily absorbed than the trivalent ones.

Laskin and Isloa (1972) studied the retention of chromium in the lungs in animals for 48 hours following 6 hours of inhalation. Neither dose levels, chromium compound, nor animal species were given. Urinary excretion of chromium increased for the first 6 hours, then gradually decreased. Fecal excretion of chromium also increased. Exposure to welding smoke from stainless steel containing from 18 to 26% chromium resulted in high after-shift urinary excretion of chromium indicating rapid absorption (Gylseth et al., 1977). A correlation between exposure to chromium and the urinary excretion of chromium was demonstrated.

6.1.2 Ingestion

Animal experiments indicate that trivalent chromium is poorly absorbed from the gastrointestinal tract, values less than 1% of an oral dose having been reported (Mertz, 1969). Chromates are absorbed at 3-6% in rats (Mertz et al., 1965), and about 2% in man (Donaldson and Barreras, 1966). There is evidence that not only the valence state of chromium in the diet but also the functional state of the intestines has bearing on absorption since the balance between trivalent and hexavalent chromium may be altered (Donaldson and Barreras, 1966). Increased absorption of hexavalent chromium has been observed in achylic patients, probably due to an absence of reduction induced by sodium chloride. These absorption values, which are based on urinary excretion after oral administration, may be underestimated as the gastrointestinal tract also takes part in chromium excretion (Hopkins, 1965).

Based on a normal urinary excretion of 2 - 10 µg/l of chromium and a daily intake of 30 - 100 µg, an absorption of 10% or more of chromium naturally occurring in food must be assumed. These values probably reflect the higher absorption of the chromium as the glucose tolerance factor.

6.2 Distribution

The distribution of chromium in the rat is dependent on the chromium compound in question (Kraintz and Talmage, 1952; Visek et al., 1953; Hopkins, 1965). All chemical forms except chromates clear rapidly from the blood. Trivalent chromium acetate or citrate are also rapidly excreted, whereas the tissue concentrations after corresponding doses of chromic chloride or chromates are higher at the same time intervals. Organs which specifically retained chromium in experiments with dose levels of 60 - 250 µg/animal were the reticuloendothelial system, the liver, the spleen and the bone marrow (Visek et al., 1953). Hopkins (1965) reported retention of chromium in the bone marrow, the spleen, the testes and in the epidydimis after injection of chromium to the rat, but the dose levels were 10 and 1 µg/kg rat weight. The organ retention of chromium after chromate injection to mice decreases with the age of the animal (Vittorio et al., 1962).

After administration of chromium as the glucose tolerance factor, the distribution is different as the highest concentration was found in the liver, followed by the uterus and the kidney (Mertz and Roginski, 1971; Mertz, 1975).

Chromium is found in the newborn and in the fetus. High natural chromium content in the mother's diet increases the chromium content in the fetus (Mertz, 1975). Transplacental transfer of chromium as the glucose tolerance factor has been demonstrated

(Visek et al., 1953; Mertz et al., 1969), and Diab and Sörenmark (1972) demonstrated transplacental transfer of chromic chloride in mice using a radiographic method.

6.3 Excretion and biological half-time

Once absorbed and bound in biological tissue chromium compounds are found in the trivalent form (Mertz, 1969). All excretion mechanisms and figures given are therefore related to this chemical form.

After parenteral administration to rats chromium is excreted predominantly in the urine. Hopkins (1965) found less than 2% of an intravenous dose in the feces 8 hours after the injection. Visek et al. (1953) found less than 20% after 4 days. Studies on the mechanism of chromium excretion by the kidneys indicate glomerular filtration followed by tubular reabsorption of up to about 60% of the filtered amount (Collins et al., 1961).

The site of the gastrointestinal excretion of chromium is not known, nor is the importance of biliary excretion (Hopkins, 1965). The fecal content of chromium may vary considerably and is mainly a consequence of ingested unabsorbed chromium compounds.

The elimination curve for chromium as measured by whole body counting has an exponential character. In rats three different components of the curve have been identified with the half-times of 0.5, 5.9 and 83.4 days, respectively (Mertz et al., 1965).

In human kinetic studies to evaluate red cell life time, a rapid excretion component related to non-erythrocyte chromium has been identified. Chromium used for labelling of erythrocytes is almost exclusively excreted in the urine. Kinetic studies of this rapid component have not been reported, and half-time is only given for chromium representing the red cell compartment (Shih et al., 1972). The kinetics of excretion of chromium as the glucose tolerance factor is not known.

7. Normal levels in tissues and biological fluids

The highest concentration of chromium in humans is found in hair, values from 200 to 2000 µg/kg having been reported

(Mertz, 1969). Schroeder et al. (1962) reported about 700 µg/kg of chromium in the lung in persons in the New York/Chicago area, other organs having lower concentrations, liver 270 µg/kg and kidney 90 µg/kg. There are geographical variations in chromium concentration as the values from the Denver area were 141 µg/kg for the lung, 30 µg/kg for the liver and 40 µg/kg for the kidney. A high concentration of chromium in the lung and a lower concentration in other organs were confirmed by Tipton and Cook (1963, 1965) both in the US and in other parts of the world.

The concentration of chromium in blood has been reported to be 20-30 µg/l with an even distribution between red cells and plasma (Feldman et al., 1967). Upon occupational exposure, the increase in blood value relates mainly to the red cells (Baetjer et al., 1959b).

A normal urinary excretion of chromium of up to about 10 µg/day has been assumed (Cornelis et al., 1975; Mertz, 1975).

The chromium concentration in all tissues decreases from birth to the age of about 10 years. After this time there is a slight increase in lung concentration, but a continuing fall in all other organs (Schroeder et al., 1962). This indicates that chromium in the lungs is a result of deposition from inhaled air, whereas chromium in food is the main source of chromium in other organs.

8. Effects and dose-response relationships

Chromium is considered essential for the maintenance of normal glucose tolerance in experimental animals and in man. Chromium as the glucose tolerance factor may have a role as cofactor for the initiation of peripheral insulin action. The exact structure of the glucose tolerance factor is not known. A complex of trivalent chromium and niacin has been suggested, but other synthetic chromium compounds also meet some of the criteria for essentiality. Chromium deficiency has been described in three animal species and in man, but a quantitative definition of the daily requirement of chromium in human nutrition has not been formulated (Mertz, 1975).

8.1 Local effects and dose-response relationships

8.1.1 Animals

Though many reports on local effects in humans have been presented, few experiments have verified these effects in laboratory animals.

Samitz and Epstein (1962) induced chromic ulcers in guinea pigs through application of various hexavalent compounds to the skin. They also demonstrated that a local skin defect is a prerequisite for the development of chrome ulcers. Mosinger and Fiorentini (1954) induced skin ulcers in different animals through application of potassium chromate to the skin. Rajka et al. (1955) produced dermatitis in guinea pigs.

"Bronchiolization" of alveoli (i.e. lining of alveolar walls by cells resembling bronchial epithelium) has been observed by different authors exposing animals to chromates (Nettesheim et al., 1971).

8.1.2 Humans

8.1.2.1 Chromic ulcers

Generally, chromic ulcers are induced by the corrosive action of hexavalent chromium. In the case of tannery workers, however, the skin ulcers may be due to chromic compounds (Maloof, 1955). When chromic acid, dichromate compounds or other hexavalent chromium compounds are deposited on the broken skin, a deeply penetrating round hole may develop (Dewirtz, 1929). Favored sites for ulcer development are the nailroot areas, over the knuckles and fingerwebs, on the back of the hands, and on the forearm (Maloof, 1955). Sometimes these ulcers are described as painful, but most of them are painless. Severe ulcerative changes penetrating to joints have been described. The ulcer heals slowly and may persist for months. The ulcer does not seem to bear any relationship to the development of allergic sensitization to chromium compounds (Edmundson, 1951).

8.1.2.2 Acute irritative dermatitis

This disease may be observed in the chromium industry, particularly in workers coming in contact with hexavalent chromium compounds. This dermatitic reaction seems to become less prominent by renewed contacts. It must be differentiated from the allergic eczematous dermatitis.

8.1.2.3 Allergic eczematous dermatitis

This allergic dermatitis was probably seen long before conclusive evidence of chromate sensitivity was given by Engelhardt and Mayer (1931). Of their workers with dermatitis, 84% reacted to the patch test with 0.5% ammonium dichromate. None of their workers reacted to a trivalent material. Gaul (1953) claimed that all chromium compounds can cause allergic skin reactions, but Nater (1962) has given evidence that allergic dermatitis is related to hexavalent chromium only. Hexavalent chromium seems to be a strong sensitizer and trivalent chromium a poor sensitizer and elicitor (Samitz et al., 1969). For the skin patch test a low concentration (0.5%) of the chromate solution is chosen, because higher ones may themselves produce acute dermatitis (Gaul, 1953; Nater, 1962).

Allergic eczematous dermatitis has been described in a variety of occupations, such as housewives, woodworkers, cement workers and limestone workers, radio factory workers, painters, polishers, furriers and others. Long a debated question, the main causal agent in cement eczema now seems to have been proven to be the trace of chromate compounds in the cement. Allergic chromium dermatitis is also widespread in persons without occupational exposure. Magnusson et al. (1968) reported the patch test, carried out mostly with an 0.5% solution of potassium dichromate, to be positive in 3 - 15% of all allergic skin reactions. These high rates might partly be caused by cross reactions with other antibodies, but it must be borne in mind that traces of chromates are ubiquitous. Therefore the hexavalent chromium may induce allergic reactions unexpectedly.

8.1.2.4 Corrosive reaction in nasal septum

Ulcerations and perforations of the nasal septum in chromate workers were described by Delpech and Hillairet (1869) and the present century has witnessed many reports on this chromium hazard. The ulcerations and perforations are acquired at workplaces with chromate or dichromate dust, or chromic acid mist. The site of the ulceration is usually about 1.5 - 2 cm from the anterior and lower margin of the septum, whence it extends backward and upward (Kleinfeld and Rosso, 1965). The ulceration seems to be caused by deposition of chromate at this site, where the mucous membrane is far less vasculated than at other parts of the septum. As soon as the mucosa is perforated the cartilage on that side of the septum loses its vascularization and tends to necrotize. With ulceration on both sides of the septum, local necrosis of the cartilage will cause perforation of the septum (Leineburg, 1955).

When exposure to chromates is discontinued before perforation has developed, the corrosive reaction usually subsides and the scar becomes crusted with mucus. Since the anterior border of the septum is never affected, the nose does not become deformed. Some workers note a disturbing "whistling" in the nose and/or an inability to control the liquid flow from the nose. No reports have been made on spontaneous healing of the established perforation.

8.1.2.5 Local effects in the lung

Mancuso and Hueper (1951) described a spotty, moderately severe but not nodular pneumoconiosis. Sluis-Cremer and du Toit (1968) have reported fine nodular pneumoconiosis, somewhat more radio-opaque than in simple coalminer's pneumoconiosis, in a few chromite workers in South Africa. Therefore, it is possible that both trivalent and hexavalent chromium compounds might cause pneumoconiosis.

Princi et al. (1962) reported 4 cases of acute upper respiratory disease with chest X-rays similar to miliary lung tuberculosis, the possibility of which was excluded. The true nature of this toxic effect, which has also been observed by other authors (Davies, 1974), presently is not clear.

8.1.2.6 Dose-response relationships

Because development of chromium ulcers seems to be dependent on a pre-existing local defect in the skin, little can be said about dose-response relationships. Development of ulcers does not seem to bear any relationship to atmospheric chromate concentration, and seems to be dependent on local deposition of the chromate compound on the skin.

Based on the existing literature it is difficult to suggest any dose-response relationship between local exposure to hexavalent chromium compounds and development of septal ulcers and perforations. The present authors have seen septal ulceration after 2 weeks and perforation after two months of exposure to approximately 1 mg zinc chromate/m^3, while we have not observed any ulcerations or perforations in workers exposed to 0.02-0.1 mg zinc chromate/m^3 up to 18 months. Kleinfeld and Rosso (1965) reported perforation in 4 of 9 workers exposed to chromic acid mist varying from 0.18 to 1.4 mg/m^3 in the breathing zone. In one of the cases perforation occurred after one month of exposure.

Sensitization dermatitis appears after variable periods of exposure to concentrations below those giving rise to primary irritant action (Klander and Combes, 1955). The dose-response relationship is therefore difficult to discuss. Pirilä (1954) determined the threshold of hypersensitivity to hexavalent chromium in 35 persons with sensitivity to chromate compounds. Using the skin patch test, he found 25 patients with a threshold at 0.1% dichromate solution, 5 with a higher and 5 with a lower threshold.

8.2 Systemic effects and dose-response relationships

8.2.1 Animals

As a secondary effect in their chromate studies on mice Nettesheim et al. (1971) observed increased subepithelial connective tissue and flattened epithelium in the large bronchi. They also observed morphological changes in tracheal and submandibular lymph nodes, atrophy of spleen and liver and ulcerations in stomach and intestinal mucosa.

Mosinger and Fiorentini (1954) administered potassium chromate to small animals by various routes, the total doses varying from 2 to 10 mg. The animals were observed from a few days up to a year. Acute gastritis and enteritis, various parenchymatous changes in the liver and kidney lesions with destruction of the epithelial cells of the tubuli were described.

Akatsuka and Fairhall (1934) exposed cats to 80-115 mg/m^3 trivalent chromium salts one hour daily for 4 months and fed another group a diet containing high amounts of chromic salts. No adverse effects were observed.

8.2.2 Humans

Typical bronchial asthma induced by inhalation of chromate dust or chromate acid fume has been reported. It seems likely that the workers are slowly sensitized and that the first symptom is an irritant cough. All reports mention a time lag of 4 to 8 hours between exposure to hexavalent chromium and the asthmatic attack. Without treatment the attack will last for 24 to 36 hours. Once the sensitization has taken place, the patient will react with a new attack upon renewed inhalation of chromates or upon subcutaneous provocation (Card, 1935; Meyers, 1950). Broch (1949) reported high incidence of bronchial asthma in a ferrochromium industry where the workers were exposed to a mixed dust.

In older literature many descriptions are given of immediate death following suicidal ingestion of high doses of potassium dichromate, suggesting a cardiotoxic effect inducing cardiac arrest. Nephrotoxic effects, described upon ingestion of smaller doses, possibly represent a tubular necrosis caused by cardiovascular shock. Liver necrosis has also been described (Brieger, 1920).

8.3 Carcinogenic, mutagenic and teratogenic effects

8.3.1 Animals

Animal experiments have not been very successful in identifying the compounds which increase the risk of bronchiogenic cancer so well documented in chromate workers. Hueper (1958) reported a small number of malignant tumors in rats after intramuscular and intrapleural administration of roasted chromite ore. Baetjer et al. (1959a) could not induce bronchiogenic cancers in mice and rats by daily exposure to 2 mg/m^3 mixed chromate dust in dust chambers. The animals were exposed four hours per day, five days per week until they died or were killed. She reported four cases of lymphosarcomas, but this finding is not confirmed by any other author. Calcium chromate has been found to induce injection-site sarcomas in mice (Payne, 1960). After intratracheal administration of calcium chromate and strontium chromate to rats Hueper and Payne (1962)found three fibrosarcomas at the end of the second year of observation, the individual chromate dose being 10-12.5 mg. Nettesheim et al. (1971) induced adenocarcinomas and adenomas in the bronchial tree of mice by exposing them to calcium chromate dust at a concentration of 13 mg/m^3 in dust chambers for 35 hours per week during their lifetime. This study is the only one in the literature demonstrating a carcinogenic effect of a chromate with inhalation as the route of exposure.

Conclusive evidence for dose-response relationships for the different carcinogenic chromium compounds in animals can not be given from the existing literature.

Some reports have been published on mutagenicity of chromates. In bacterial models Venitt and Levy (1974) have shown that simple hexavalent chromate salts of sodium, potassium and calcium work as mutagens. This finding is supported by Nishioka (1975) using potassium chromates. Transformations of cell cultures treated with calcium chromate were reported by Fradkin et al. (1975).

Reports on teratogenic effects of chromium have not been published.

Hexavalent chromium reacts easily with nucleic acids, most likely bringing about a reduction to trivalent chromium and complex formation with the nucleic acids. Some nucleic acids contain high concentrations of chromium and highly purified RNA fractions contain considerable amounts of chromium. The function of chromium in RNA is not known, but it might be of importance for structure stabilising. Using BHK fibroblasts Levis and Buttignol (1977) demonstrated inhibition of DNA synthesis induced by a 10^{-4}M concentration of $K_2Cr_2O_7$ and almost complete and irreversible inhibition of DNA synthesis induced by a 10^{-3}M concentration of the same salt (Levis et al., 1977).

8.3.2 Humans

Newman (1890) reported adenocarcinoma in the inferior turbinate bone of the nose in a worker who had been involved in chromate pigment production for 30 years. Lehmann (1932) was the first to discuss a connection between exposure to chromates and development of lung cancer. During the 1930's many reports were published in Germany on this association, and in 1936 the German health authorities officially recognized lung cancer as a possible occupational disease associated with chromate dust exposure. Later many papers have been published in the US (Taylor, 1966), England (Bidstrup and Case, 1956) and other countries, and in all approximately 250 "chromate lung cancers" have been reported. Increased incidence of cancer in chromate workers is reported as late as in 1975 (Langård and Norseth, 1975), the observed to expected ratio with more than three years of exposure being 38.

American studies are definitely indicative of highly excessive lung cancer rates among chromate producers and chrome pigment makers (Machle and Gregorius, 1948; Mancuso and Hueper, 1951; Taylor, 1966). Machle and Gregorius observed 193 deaths from all causes among 1445 workers in factories producing chromates.

Of the deaths 66 were caused by cancer, 42 of which were lung cancer.

In a similar plant, Mancuso (1975) reported that 23.7% of the deaths were caused by lung cancer, lung cancer causing 62.1% of all cancer deaths. Where lung cancer is concerned, epidemiological studies on occupationally exposed persons have reported observed/expected ratios from 5 to 40. There seems to be no doubt that hexavalent chromium plays an important carcinogenic role in these high figures. Increased incidence of cancer at other sites (Taylor, 1966), particularly the gastrointestinal tract, has been reported (Enterline, 1974). However, some of these studies do not rule out other carcinogens as possible additional causes.

In chromate lung cancers, the highest incidence is at the age of 50 to 52 years, about 5 years earlier than the highest incidence of lung cancer in heavy smokers. The time between the first chromate exposure and the time of diagnoses varies much from report to report, but a mean seems to be somewhere between 15 and 17 years (Baetjer, 1950).

Pokrovskaya (1973) reported increased incidence of lung cancer and cancer at other sites in workers in chromium ferroalloy production, i.e. in the production of non-hexavalent chromium, but the workers were also exposed to other carcinogens. Mancuso (1975) indicated that the carcinogenic effect extends to all forms of chromium and is directly related to the total amount of chromium taken into the respiratory system. However, this study is a cohort study in which the cohorts are not based on exposure to exclusively trivalent, respectively hexavalent chromium compounds. There are no studies available today which conclusively show that chromium compounds other than hexavalent ones are carcinogenic, although a carcinogenic effect of other compounds cannot be excluded.

D.4 Biological interactions

In the hexavalent state, chromium is a strong oxidizing agent and reacts readily with organic materials, leading to a reduction to the trivalent form. No complexes are known in which hexavalent chromium can be stabilized against reduction.

All biological interactions of chromates seem to result in reduction to the trivalent form and coordination to organic molecules. So far, all the toxic effects of hexavalent chromium seem to be related to the strong oxidizing action of chromates. Trivalent chromium may play an important role in the activity of different enzymatic reactions such as thromboplastic activity, beta glucuronidase activity and bacterial urease activity.

Indications of interactions of chromium compounds with substances in cigarette smoke are few. Fisher and Riekert (1959) mentioned that among 38 chromate producers with lung cancer only 2 were non-smokers. Bidstrup and Case (1956) reported that all chromium workers in their study who died from lung cancer were heavy smokers. They concluded that the increase of carcinoma of the lung that would be expected if the smoking habits of their groups differed so much from the general population's that all the workers fell into the category of heavy smokers, would not satisfactorily account for the increase which they had observed.

9. Preventive measures, diagnosis, treatment, and prognosis

Lavage with magnesium carbonate or lead acetate mixed in water or ingestion of quantities of milk or other emulgations have been advised in cases of attempted suicide by chromic acid ingestion.

Acute asthmatic attacks caused by chromates should be treated like other asthmatic attacks. Persons with an atopic history should avoid working in the chromate industry. Once an allergic skin reaction has developed, the person should discontinue his contact with the chromium-containing agent.

Keeping the chromate concentration in the working atmosphere below the TLV is the best prevention against the local and systemic effects of hexavalent chromium. Wearing gloves which are not too warm is absolutely necessary for workers handling chromic acid or dichromates. Wounds on the hands and forearms should be covered. Personal hygiene is very important for workers exposed even to very low chromate concentrations. Daily washing of the inside of the nose combined with covering the nasal septum with zinc or barium ointment should be sufficient to avoid ulcerations and perforation of the septum.

Treatment of chromium ulcers has not been very successful. Discontinuing the local exposure to hexavalent chromium seems to allow the ulcer to heal within a few weeks, but persistence for years has been described. An ointment containing 10% sodium and calcium EDTA, or a 10% solution of fresh ascorbic acid, seems to give some protection to the skin.

Some investigators recommend that persons below 35 years of age not be employed in the chromate industry. As a preventive measure, X-rays of the lungs yearly or more often have been advised. Promising results using a three-day "pooled" sputum cytology test for the early diagnosis of bronchial cancer have been reported.

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COBALT

Carl-Gustav Elinder and Lars Friberg

1. Abstract

Gastrointestinal absorption of cobalt can be estimated to be about 25%, with wide individual variation; excretion takes place mainly via the urinary tract. The major part of absorbed cobalt is excreted within days but a small part, approximately 10%, has a biological half-time of at least a couple of years.

Cobalt is essential as an integral component of vitamin B_{12}.

Addition of cobalt to beer has caused endemic outbreaks of cardiomyopathy among heavy beer drinkers, resulting in a number of fatalities. Myocardial degeneration and electrocardiographic changes have also been seen in laboratory animals after repeated intramuscular injections of cobalt.

Industrial exposure has given rise to pneumoconiosis, in some cases of an invalidating nature. Different pulmonary defects have also been reported in experimental animals.

In rats cobalt has given rise to sarcoma at the site of injection and in chicken eggs teratogenic effects have been seen to result from injection of cobalt.

2. Physical and chemical properties

Cobalt, Co; atomic weight 58.9; atomic number 27; density 8.9; melting point 1495°C; boiling point 2870°C; crystalline form silver gray metal, cubic; oxidation state 2,3.

Compounds taken up here are cobalt oxide, cobalt tetraoxide, cobalt chloride, cobalt sulfide and cobalt sulfate.

The pure metal is hard and brittle and has magnetic properties.

3. Methods and problems of analysis

The first methods for analysing cobalt in biological materials, which were introduced during the 1940's, were colorimetric. Detection limits of 0.1 mg Co in 20 l of blood and 0.05-0.10 mg/l in blood have been reported for two respective colorimetric methods (Stone, 1965; Hubbard et al., 1966).

During the 1960's emission spectrographs, polarographs, X-ray fluorescence and atomic absorption spectrophotometry were introduced. Employing AAS, Fishman and Midgett (1967) gave a detection limit of 0.05 mg/l in water, and Sachdev et al. (1967) 0.03 mg/l. Using sequential extraction of cobalt from samples with low concentrations, Delves et al. (1971) increased the sensitivity several-fold. A neutron activation method described by Cornelis et al. (1975) could detect cobalt in urine in concentrations below 0.5 µg/l.

No data on the accuracy of methods for the determination of cobalt in body tissues and fluids are available.

4. Production and uses

4.1 Production

Cobalt is a relatively rare element composing about 0.001% of the earth's crust. The most important minerals are arsenites, i.e. smaltites, cobaltite, sulfides and oxides (Stokinger and Wagner, 1958; Kaplun, 1963).

The consumption of cobalt and its compounds has greatly increased in recent years, at a rate of about 5% per year. In 1972 the world production was 293,000 tons (Corrick, 1972). That same year, the Republic of Zaire produced 56% of the annual mine output, followed by Zambia with about 5%.

4.2 Uses

The manufacture of cobalt-blue colored pottery and glass antedates the Christian era, but it was not until the 20th century that cobalt was introduced as an alloy. Advantages of cobalt alloys are high melting point, strength and resistance to oxidation. In 1971 about three-fourths of the U.S. consumption of cobalt was in the production of steel and alloys (Corrick, 1972). The remaining one-fourth went to salts and driers.

A marginal part of the refined cobalt is used in fertilisers, since a low cobalt concentration in soil may cause cobalt deficiency among sheep and cattle. Cobalt is also used in human medicine in the treatment of certain iron-resistant anemias (Coles, 1955; Shuttleworth et al., 1961; Schirrmacher, 1967).

5. Environmental levels and exposures

5.1 General environment

5.1.1 Food and daily intake

Colorimetric and neutron activation analyses of food indicate that the average daily intake of cobalt is 5-40 μg (Harp and Scoular, 1952; Ripak, 1961; Hubbard et al., 1966; Wester, 1974a). Even though there is good reason to believe that these values represent an average normal daily intake, some contradictory data, showing considerably higher values, have emerged in some studies employing emission spectroscopy and AAS (Tipton et al., 1966; Schroeder et al., 1967). Certain seafoods contain higher than average concentrations of cobalt (Schroeder et al., 1967).

In 13 commercial beers analysed by Stone (1965) using a colorimetric method, cobalt usually measured well below 0.1 mg/l unless the metal had been added in processing, up to 1.1 mg/l being recorded in such cases.

5.1.2 Water, soil and ambient air

Drinking water has shown low concentrations of cobalt, usually between 0.1–5 µg/l (Schroeder et al., 1967; Punsar et al., 1975). In inland waters, about the same concentrations will be found (Nix and Goodwin, 1970; Paus, 1971). Sea water has been shown to contain less cobalt than fresh water (Vinogradova and Prokhorova, 1968; Piper and Goles, 1969).

In U.S. soil, cobalt ranges from 0.1 to 13 mg/kg (Schroeder et al., 1967).

In ambient air the concentration of cobalt is usually low. Tabor and Warren (1958) found detectable amounts of cobalt (>0.3 ng/m^3) in only 90 out of 750 air samples taken from 28 sampling stations in the U.S., using a semiquantitative spectrographic method. Using neutron activation, Brar et al. (1970) found cobalt in Chicago air ranging from 0.3 to 23 ng/m^3.

5.1.3 Cigarettes

Cobalt in cigarettes has been studied by means of neutron activation by Nadkarni and Ehmann (1970). The tobacco, on an average, contained 0.5 mg Co/kg dry weight. When the cigarettes were smoked in a standard smoking machine, 0.5% was found in the mainstream.

5.2 Working environment

Cobalt may be released into the air during the production of cobalt oxide and in the processing of hard metals. From the USSR, Kaplun (1963) reported occupational air concentrations reaching 10 and even 100 mg/m^3 in a cobalt oxide plant. The highest average in a tungsten carbide industry studied by Fairhall et al. (1949) was 1.7 mg/m^3.

6. Metabolism

Cyanocobalamin or vitamin B_{12}, a cobalt-containing tetrapyrrolic ring, is essential in mammalian nutrition. The recommended daily intake of B_{12} for an adult is 3 µg, corresponding to 0.12 µg of cobalt (Food and Nutrition Board, 1974). Ruminant animals in contrast to man and some other monogastric mammals have intestinal microflora which utilize cobalt in the formation of vitamin B_{12}. Deficiency states among ruminants have been reported from various countries (Young, 1949; Beeson, 1950. No function for cobalt in human nutrition other than as an integral part of the vitamin B_{12} molecule has been established (Underwood, 1973). Concerning the absorption of B_{12}, human beings require the interaction of a glucoprotein, "intrinsic factor", which is formed in the stomach. In the presence of this factor absorption is about 70%, but without it, less than 2%. The total body vitamin B_{12} content in a normal, i.e. non-deficient, human is about 5 mg (Wintrobe and Lee, 1970).

6.1 Absorption

In the following, only forms of cobalt other than vitamin B_{12} will be dealt with. No data on respiratory absorption of cobalt are available.

6.1.1 Animals

The gastrointestinal absorption (^{60}Co as chloride) in rats has been estimated to be around 30% (Comar and Davis, 1947; Carlberger, 1961; Taylor, 1962). Increasing oral doses of cobalt decreased the relative absorption (Taylor, 1962).

Iron deficiency increases the absorption of cobalt, and simultaneous administration of iron and cobalt reduces the absorption of cobalt (Schade, 1970).

6.1.2 Humans

Gastrointestinal absorption is reported to vary from 5-45%. Ripak (1961) studied cobalt balance in three schoolchildren. The daily intake was calculated to be 41 µg; out of this figure 92-95% was found in feces and 4-5% in urine. When radioactive ^{60}Co as $CoCl_2$ was given orally to humans, the average absorption was calculated at 5-44%, these figures based on the amount of unabsorbed cobalt remaining in the feces (Valberg et al., 1969; Smith et al., 1972).

Absorption and/or excretion may be influenced by amount of cobalt given and by nutritional factors. For example, the 48 hour urinary excretion of perorally given labelled cobalt ranged between 1% and 16% depending on amount of cobalt given, fasting or non-fasting state of subjects or addition of albumin to the diet (Paley and Sussman, 1963).

6.2 Distribution

6.2.1 Animals

Cobalt given either parenterally or per os does not show any prominent accumulation in any specific organ. The highest concentrations are found in liver, adrenals and thyroid (Copp and Greenberg, 1941; Comar et al., 1946; Comar and Davis, 1947).

In dogs exposed to ^{60}Co oxides (Co_3O_4 and CoO) the highest cobalt concentrations were recorded in the lung after 140 days, followed by kidney and liver (Barnes et al., 1976).

6.2.2 Humans

In exposed human beings, liver shows the highest concentration of cobalt, followed by the kidneys. Employing intravenous administration of radioactive $CoCl_2$, Smith et al. (1972) estimated the liver to hold about one-fifth of the total body burden of cobalt.

6.3 Excretion

6.3.1 Animals

Parenterally administered cobalt is excreted mainly in urine, about 90% in 48 hours (Copp and Greenberg, 1941; Comar et al., 1946). Biliary excretion in dogs given $^{57}CoCl_2$ intravenously was 5% in 72 hours (Sheline et al., 1946).

6.3.2 Humans

The main part of parenterally given cobalt will be found in the urine. Kent and McCance (1941) gave daily cobalt injections of 2.6 mg for 5 days to human volunteers. Two days after the last injection, 15% of the given dose had been recovered in urine and 5% in feces. A similar study on human volunteers was performed by Smith et al. (1972). After 8 days 56% and 11% of the given dose had been excreted in urine and feces respectively.

6.4 Biological half-time

6.4.1 Animals

In dogs exposed to ^{60}cobalt oxide aerosols, Co_3O_4 has been shown to have a markedly slower elimination from the lung compared with CoO; remaining lung burdens after 8 days postexposure were 85% and 10% respectively. After an initial fast elimination of about 50% of body burden the biological half-time of ^{60}Co was estimated at around 60 days and 35 days for Co_3O_4 and CoO respectively (Barnes et al., 1976).

6.4.2 Humans

Several works concerning the biological half-time of cobalt have been published (Morsy and El-Assaly, 1970; Newton and Rondo, 1970; Smith et al., 1972). A fast excretion phase takes place, followed by a pronounced cobalt retention.

Morsy and Al-Assaly (1970) studied the retention of ^{60}Co accidentally swallowed by a worker. The body burden was estimated by body scanning. Three components of half-times were calculated, amounting to 0.5, 2.7 and 59 days respectively. These values correspond to about 5% retention of total ingested dose after two days and 1% after 30 days. The two initial rapid elimination components are partly explained by fecal elimination of unabsorbed cobalt.

The retention of ^{60}Co given intravenously has been studied by total body counting for periods up to 1,000 days. Following a rapid initial clearance within days of about 90% of a given dose, 10% was eliminated with a biological half-time of about 2 years (Smith et al., 1972).

The behavior of ^{60}Co in men for up to 11 years after accidental inhalation was followed by Newton and Rundo (1970). After a fast clearance of the main part of the absorbed cobalt, the rest, about 10%, had a biological half-time in the chest as well as in whole body of 5-15 years.

7. Normal levels in tissues and biological fluids

In autopsy studies, liver has had the highest concentration of cobalt, individual values ranging from 0.01 to 0.07 mg Co/kg wet weight (Forbes et al., 1954, a colorimetric method; Parr and Taylor, 1964, neutron activation; Sumino et al., 1975, AAS). In serum from normal humans the cobalt concentration has been found to be about 0.4 μg/l (Wester, 1974b, employing neutron activation). In urine individual concentrations ranging from 0.5 to 2.2 μg/l have been reported (Wester, 1974b; Cornelis et al., 1975).

With regard to vitamin B_{12}, the total liver content is estimated at 1.7 mg, which corresponds to a cobalt concentration in 1.7 kg liver of 0.04 mg/kg wet weight. This indicates that the cobalt found in human liver to a great extent might be in the form of vitamin B_{12}.

8. Effects and dose-response relationships

8.1 Local effects and dose-response relationships

8.1.1 Animals

Inhalation of high concentrations of cobalt causes advanced edema and multiple hemorrhages (Harding, 1950; Höbel et al., 1972). Twelve months after a single intratracheal injection to rats of 50 mg cobalt in the form of metal particles, Schepers (1955) reported diffuse central fibrocellular infiltration of the lungs. In contrast, three intratracheal introductions of 50 mg cobalt oxide produced an acute response, but within one month the lungs were normal.

Kerfoot et al. (1975) exposed miniature swine to pure cobalt metal powder at air concentrations of 0.1-1.0 mg Co/m^3 for 6 hours per day, five days a week. After three months a progressive decrease in ventilatory lung compliance was detected among exposed animals (35, 23 and 20 cc/cm H_2O for controls, low cobalt and high cobalt groups respectively). Electron microscopy demonstrated thickening and collagenisation of alveolar septa in lung biopsies.

Divalent inorganic compounds are more toxic than trivalent ones (Fredrick and Bradley, 1946; Levina and Loit, 1961; Van Liew and Chen, 1972).

Dickson and Bond (1974) described five cases of fatal cobalt poisoning in cattle. The average liver concentration of cobalt was 58 mg Co/kg dry weight (about 15 mg/kg wet weight) compared with 0.1 mg/kg dry weight among healthy cattle.

A significant reduction of growth in ducklings nourished with a diet enriched with 0.2% $CoCl_2$ was recorded by Paulov (1971). Mice drinking cobalt sulfate solution, 47 mg Co/kg, had a twofold higher mortality in 2 1/2 months when exposed to encephalomyocarditis virus compared with controls drinking demineralized water (Gainer, 1972).

8.1.2 Humans

8.1.2.1 Respiratory effects

Occupational exposure to cobalt in air occurs mainly in the tungsten and cemented carbide industries in which several cases of pneumoconiosis have been reported. The disease is reported to have been produced by air concentrations of cobalt of 0.1-2 mg/m^3 (Miller et al., 1953; Anonymous, 1968; Dorsit et al., 1970; Coates and Watson, 1971). Cobalt is also considered to be an etiological agent in "hard metal" pneumoconiosis: i.e., that occurring in hard metal industries. Hard metal is manufactured by a process of powder metallurgy from tungsten and carbon with cobalt as a binder. Titanium and tantalum are sometimes also added (Bech et al., 1962; Joseph, 1968).

In 1953 Miller et al. described three cases of pneumoconiosis in a tungsten carbide tool industry where the exposure to cobalt powder, oxide or salt, had varied between 0.1-0.2 mg Co/m^3 for 2.5-7 years. It was stated that these three men were the only workers with pneumoconiosis out of about 1,500 men with similar exposure. Coates and Watson (1971) examined workers exposed to cobalt powder as they were engaged in the grinding and manufacturing of tungsten carbide. They described two types of respiratory disease. The first was characterised by cough, wheezing and shortness of breath and was relieved by removal from work. This type was suggested to have an allergic background. The second, manifested by 12 workers, was a progressive interstitial lung disease. Eight cases were fatal, and microscopic examination of the lungs showed interstitial infiltration and fibrosis. Exposure time for these twelve workers ranged from 1 month to 28 years and concentrations of cobalt exceeded 0.1 mg/m^3.

8.1.2.2 Skin effects

The existence of cobalt allergy is well documented; the dermatitis evoked is of an erythematous papular type (Schwartz et al., 1945; Marcussen, 1963; Raben et al., 1966; Camarasa, 1967).

8.2 Systemic effects and dose-response relationships

8.2.1 Animals

8.2.1.1 Effects on blood

Cobalt has an erythropoietic action, increasing blood volume and total erythrocyte mass considerably in several animal species (Brewer, 1940; Tribukait, 1963; Liotti et al., 1971). It has been suggested that an erythropoietic factor is released from the spleen (Smith et al., 1972).

Intraperitoneal injections of cobalt also result in large increases of serum lipids, mainly the triglyceride fraction (Caplan and Bloch, 1963; Zarafonetis et al., 1965). Fiedler et al. (1971) demonstrated that cobalt compounds cause hypocoagulability.

8.2.1.2 Myocardial effects

Subsequent to the reports of cardiac failure in drinkers of beer with added cobalt in Quebec (Section 8.2.2.2), a large number of animal studies have shown that repeated intramuscular injection of cobalt on the order of 5 mg/kg to rats produces myocardial degeneration. In an experiment using electron microscopy, slight changes were seen after only one injection (Hall and Smith, 1968; Lin and Duffy, 1970). It is claimed that essential phospholipids in doses of 7 mg/day protect rats against some myocardial effects (Wojcicki et al., 1973). Also electrocardiographic changes were reported among exposed animals (Mohiuddin et al., 1970).

8.2.1.3 Effects on thyroid gland

Animal studies have confirmed the observation made in humans that cobalt is giotrogenic. Nivikova (1963) noted a decreased ability of the thyroid to concentrate iodine among rats given a total of 150 μg Co/day as $CoCl_2$ in food.

8.2.1.4 Effects on the pancreas

Single injections of cobalt produce transient hyperglycemia. Twenty-four hours following an intravenous injection of 200 mg $CoCl_2$ to dogs weighing from 15 to 20 kg a complete absence of alpha cells in many of the pancreatic islets was observed (Lazarus et al., 1953; Hultqvist, 1959).

8.2.1.5 Effects on the kidney

Daily intraperitoneal injections of 30 mg Co/kg (as $CoCl_2$) to guinea pigs gave rise to protein and sugar in urine after two days. Anuria developed during the sixth and seventh days. Histopathological examination showed tubular degeneration (Beskid, 1963).

8.2.2 Humans

8.2.2.1 Effects on blood

Cobalt is used in medical treatment of anemias and has an erythropoietic effect. Polycythemia has also been reported in heavy drinkers of cobalt-contaminated beer (Morin and Daniel, 1967; Kesteloot et al., 1968; Alexander, 1972).

8.2.2.2 Myocardial effects

Endemic outbreaks of cardiomyopathy with mortality rates up to 50% have been described among heavy beer drinkers. Common findings were heart failure, polycythemia and thyroid lesions. These outbreaks have been reported in Quebec, Canada, Minneapolis, USA and Belgium (Morin and Daniel, 1967; Kesteloot et al., 1968; Alexander, 1972). The syndrome first appeared about one month after a new brewery process had been introduced wherein cobalt sulfide was added to beer in order to improve the stability of the foam. It may be calculated that a really heavy beer drinker consuming up to 10 liters of beer/day could get an additional intake of cobalt in the neighborhood of 10 mg/day. Although this figure is excessively high compared with nutritional standards, it is not as large as doses given in the treatment of anemias. It has been suggested that the syndrome was multicausal, other factors probably having been malnutrition and excessive alcoholic consumption.

Morin et al. (1967) studied some of these beer drinking patients and reported typical signs of heart failure with shortness of breath, ankle edema and in some cases, cyanosis and ECG-changes. Upon autopsy Bonenfant et al. (1969) found striking myocardial fiber degeneration when heart tissue was examined histologically. In a retrospective study, hearts of victims were shown to have about 10 times the cobalt concentrations of controls, 0.5 mg/kg wet weight and 0.04 mg/kg wet weight, respectively (Sullivan et al., 1968).

One case of myocardial toxicity has been associated with industrial exposure. Barborik and Dusek (1972), upon autopsy of a 41 year-old cobalt-exposed worker, found a microscopic picture resembling that seen among cobalt beer drinkers. The heart, lungs, liver, spleen and kidneys contained about ten times the cobalt concentration found in two controls (e.g. heart, 0.37 vs 0.05 and 0.02 mg Co/kg). Exposure time and exposure levels were not given.

8.2.2.3 Effects on thyroid gland

Goiter is a well-known side effect of cobalt therapy in the medical treatment of certain anemias. A reduced ^{131}Iodine concentration capacity was seen in patients given 20-30 mg Co/day (Kriss et al., 1955; Roche and Layrisse, 1956; Schirrmacher, 1967). Usually these adverse effects are regarded as reversible. Thyroid changes were also noted among the Quebec beer drinkers (Roy et al., 1968). Upon autopsy, 11 out of 14 examined glands showed significant changes, with reduced size of follicles.

8.3 Carcinogenic and teratogenic effects

Single and repeated subcutaneous injections of cobalt powder and salts in doses of 10 to 30 mg to rats may cause sarcomata at the site of injection (Heath, 1956; Gilman and Ruckbauer, 1962). About one year after a single injection of 20 mg CoO into rat thigh muscles, 50% responded with sarcomas. Mice, however, given twice as high doses did not develop any malignant tumors (Gilman, 1962). Herich (1965) found some chromosome abnormalities in root tips exposed to cobalt.

Slight teratogenic effects have been induced in chicken eggs by injections of 0.4-0.5 mg of cobalt (Adhikari, 1967; Kury and Crosby, 1968).

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COPPER

Magnus Piscator

1. Abstract

The absorption of ingested copper in food, being about 50 %, is normally regulated by homeostatic mechanisms. Copper is mainly stored in liver and muscles. Excretion is mainly via the bile and only a few percent of the absorbed amount is found in urine. The metabolism of copper is influenced by molybdenum. The biological half-time in human beings is about 4 weeks.

Copper is an essential metal.

Accidental ingestion of large amounts of copper salts causes gastrointestinal disturbances. Inhalation of copper fumes may cause metal-fume fever. Chronic copper poisoning has not been described in normal human beings. Systemic effects, especially hemolysis, liver damage, and renal damage, have been reported after ingestion of large amounts of copper salts, but recovery has usually been rapid upon removal from exposure and treatment. In industry, copper exposure is common, but chronic effects have not been reported. Lung changes have been reported in vineyard workers spraying vines with copper sulfate solutions. Since other compounds may contribute, the role of copper in these cases has not been fully elucidated. Endogenous copper poisoning occurs in Wilson's disease, an inborn error of metabolism.

For general reviews on copper see Adelstein and Vallee (1961), Schroeder et al. (1966), O'Dell (1976) and Underwood (1971).

2. Physical and chemical properties

Copper, Cu, atomic weight 63.5; atomic number 29; density 8.9; melting point 1083.4^{0}C; boiling point 2.567^{0}C; crystalline form reddish metal, cubic; oxidation state 1,2. Only two compounds copper sulfate and copper acetate, will be specified in this chapter. Copper is malleable, ductile and a good conductor of heat and electricity, second only to silver with regard to the latter.

3. Methods and problems of analysis

Reliable methods for determination of copper in biological material have been available for many decades. The most common colorimetric method allows sodium diethyl dithiocarbamate to form a yellow complex with copper, which can be extracted into an organic solvent, usually amyl alcohol (van Ravesteyn, 1944; Lyke, 1965). Blood and urine values obtained with this method agree well with recently published results obtained with more modern techniques.

Emission spectroscopy (Butt et al., 1964), neutron activation (Brune et al., 1961; Danielsen and Steinnes, 1970; Cornelis et al., 1975), atomic absorption spectrophotometry (Kubota et al., 1968; Matousek and Stevens, 1971; Stegavik, 1975; Dorn et al., 1975; Korkisch and Sorio, 1975) and electrochemical methods, e.g. pulse polarography, anodic stripping voltametry (Whitnack and Sasselli, 1969; Sinko and Dolezal, 1970; Abdullah and Royle, 1972; Sinko and Gomiscek, 1972; Rojahn, 1972; Colovos et al., 1973) have all been used for the determination of copper in biological and environmental samples. Concentrations of 0.01-0.1 mg/kg can easily be determined by such methods. Atomic absorption spectrophotometry, the most common method at present, may detect a few ng of copper, especially with flameless atomization (Matousek and Stevens, 1971), making it possible to use microliter volumes of blood and plasma.

There are no interlaboratory comparisons of different methods available, but the good agreement between results obtained in e.g. blood and urine in different areas in the world during many decades suggests that copper can be accurately determined by several methods in most materials.

4. Production and Uses

4.1 Production

The principal copper ores are cuprite, malachite, azurite, chalcopyrite and bornite. Sulfide ores constitute about 75 %

of the total production. Copper may even occur in nature as a pure metal, which accounts for about 6 % of used deposits. Oxides and carbonates may occur in the ores. Copper ores also contain other metals, such as zinc, cadmium and molybdenum. Copper is obtained from the ores by smelting, leaching or electrolysis.

The world production in 1970 was estimated at 6,000,000 tons.

4.2 Uses

The primary use of copper, accounting for approximately half of the production, is in electrical equipment. Copper is also a component of many alloys where it may occur together with other metals, such as silver, cadmium, tin and zinc. Other important uses for copper are in plumbing and heating. Copper salts may serve as pesticides.

5. Environmental levels and exposures

5.1 Food and daily intake

The daily intake of copper from food generally varies from about 1 to about 3 mg, corresponding to about 15 to 45 ug/kg b.w. in adults (Adelstein and Vallee, 1961; Schroeder et al., 1966; Tipton et al., 1966, 1969; Robinson et al., 1973; Alexander et al., 1974; Klevay, 1975). Some low protein and low calorie diets may give less than 1 mg (Klevay, 1975). The daily requirements have been estimated to be about 30 ug/kg b.w. for adults, 40 ug/kg b.w. for older children and 80 ug/kg b.w. for infants. (WHO, 1973). Meat, internal organs, fish and green vegetables are good sources of copper.

Cereals contain less copper and milk is relatively poor in copper (WHO, 1973). Concentrations in food are generally around 1 mg/kg. Copper-poor items such as milk usually contain less than 0.1 mg/kg.

5.2 Water, soil and ambient air

In seawater, most reports have indicated concentrations from 1-5 ug/l (Abdullah et al., 1972; Rojahn, 1972; Preston et al., 1972). In American rivers concentrations ranging from 0.83-105 μg/l (median 5.3) have been reported (Durum et al., 1971). In drinking water very large variations may occur depending on type of water e.g. hardness and pH and types of pipes and taps. Concentrations from a few μg to more than 1 mg/l have been reported (Schroeder et al., 1966; Stegavik, 1975), meaning that drinking water may sometimes add a considerable amount of copper to the daily intake obtained via food. Natural copper concentrations in soil vary from 2-100 mg/kg dry weight (Bowen, 1966). Air levels of copper in the U.S. have been reported to vary from 10-570 ng/m^3, the highest values being found in urban areas (Schroeder, 1970; Kneip et al., 1970). At the South Pole the average copper concentration in air was 0.036 ng/m^3 (Zoller et al., 1974).

6. Metabolism

6.1 Absorption

6.1.1 Inhalation

There are no data on absorption rates of copper compounds after inhalation from animal or human studies.

6.1.2 Ingestion

The gastrointestinal absorption is normally regulated by the copper status in the body. Studies using radioactive copper on rats indicated that small doses (<1 μg) were absorbed to more than 50 %, but that increasing doses were absorbed to a relatively lesser extent (Owen, 1964). In contrast to most other metals copper seems to be absorbed to a large extent in the stomach, as shown in rats (Van Campen and Mitchell, 1965).

Studies using ^{64}Cu and ^{67}Cu on seven human subjects showed an average absorption of 57 % (Strickland et al., 1972b). Results from a balance study on four women indicated an absorption between 49 and 65 % (Robinson et al., 1973). Kinky hair disease (Menkes' steely hair syndrome, Menkes, 1962) is an inborn error of metabolism in which an abnormally low absorption of copper, about 12 %, causes low tissue levels of copper (Dekaban et al., 1975).

6.2 Distribution

Absorbed copper is stored mainly in liver, heart, brain, kidney and muscles, where the highest concentrations have been found both in experiments on animals and in human beings (Adelstein and Vallee, 1961; Owen, 1965; Schroeder et al. 1966; Sandstead et al., 1970; Sumino et al., 1975). Copper is transported primarily with a high molecular weight protein, ceruloplasmin, which is produced in the liver, and also functions as an oxidase. In the tissues and blood cells, copper is found bound to proteins, many being enzymes.

6.3 Excretion

The main excretion route is via the bile as shown in animals and in human beings (van Ravesteyn, 1944; Owen, 1964; Walshe 1967; Strickland et al., 1972a). In rats a minor part of the copper in bile is reabsorbed (Owen, 1964; Cikrt, 1973). Whether or not this is true for humans as well has not been shown. Some copper may be excreted via sweat (Hohnadel et al., 1973). Excretion via the urine is low in animals and in man. Less than 1 % of an intravenous injection of a tracer dose of ^{64}Cu as the acetate had been excreted via the urine within 72 hours by normal subjects. In the same time period about 9 % had been excreted via feces (Tauxe et al., 1966). The urinary excretion of copper is influenced by the molybdenum intake of humans. A low molybdenum concentration in the diet causes a low excretion of copper and a high intake of molybdenum provokes a considerable increase in excretion of copper (Kovalskii et al., 1961; Deosthale and Gopalan, 1974).

Wilson's disease, an inborn error of metabolism, heightens the urinary excretion of copper considerably. In a comparative balance study, a subject with Wilson's disease excreted about 90 μg/day whereas a normal control excreted about 20 μg/day when they had the same dietary intake (Tu et al., 1965). On the other hand the gastrointestinal excretion is considerably greater in normal persons than in patients with Wilson's disease (Tauxe et al., 1966; Strickland et al., 1972a) or with kinky hair disease (Dekaban et al., 1975). The urinary excretion of copper increases in some other diseases, especially in the nephrotic syndrome (Kleinbaum, 1965).

6.4 Biological half-time

From data by Tauxe et al. (1966) who gave an intravenous injection of radioactive copper to normal human beings, it can be seen that after 72 hours only about 10 % of the given dose had been excreted in urine and feces together, indicating a biological half-time of several weeks. External measurements of liver content of copper showed essentially no changes here during the 72-hour period. The half-time of injected copper was found to be about 4 weeks in normal subjects (Strickland, 1972a, 1972b; Dekaban et al., 1975) whereas it was much longer in subjects with Wilson's disease (Strickland et al., 1972a).

7. Normal levels in tissues and biological fluids

The liver of the newborn has concentrations of copper of about 30 mg/kg wet weight, but during the first year of life its level decreases to between 5 and 10 mg/kg wet weight. This level is then relatively constant throughout the life-time (Schroeder et al., 1966). In the newborn renal levels of copper are about 4 mg/kg wet weight and in the adult around 3 mg/kg wet weight (Schroeder et al., 1966). Similar results on copper concentrations in the adult liver and kidney have been reported by Anke and Schneider (1971), Voors et al. (1975) and Sumino et al. (1975).

The normal concentrations of copper in whole blood, plasma and erythrocytes have been reported to be around 1 mg/l (Brune et al., 1961; Butt et al., 1964; Lyko, 1965; Olehy et al., 1966; Kubota et al., 1968; Niedermeier and Griggs, 1971; Schenker et al., 1971; Höhn et al., 1972; Wester, 1973; Heineman, 1974; Kolaric et al., 1975). The copper content of serum is subject to variations, especially pronounced in women. A considerable increase, up to more than two-fold, in copper levels in serum may take place during pregnancy (Höhn et al., 1972). The intake of oral contraceptives also increases the level of copper in serum (Schenker et al., 1971; Heineman, 1974). Behind such increases in serum copper in women is an increase in serum ceruloplasmin because of the hormonal influence on the synthesis of ceruloplasmin.

Data from children in different age groups indicate that about 2 µg/kg b.w. is excreted daily via the urine up to the age of 12 (Kleinbaum, 1964; Alexander et al., 1974). In adults daily excretion has been found to be less than 100 µg/day, usually around 20 µg/day (van Ravesteyn, 1944; Lyko, 1965; Deosthale and Gopalan, 1973; Robinson et al., 1973; Wester, 1974a, 1974b; Cornelis et al., 1975). In a balance study Robinson et al. (1973) found that on an intake of about 2 mg of copper/day the urinary excretion varied between 11-48 µg/day.

8. Effects and dose-response relationships

Copper is an essential element. It is an essential part of several enzymes, e.g. tyrosinase, which is necessary for the formation of melanin pigments, cytochrome oxidase, superoxide dismutase, amine oxidases, and uricase. Copper is essential for the utilization of iron in the formation of hemoglobin. In animals molybdenum has been shown to influence the tissue and blood levels of copper (Huisingh et al., 1973; O'Dell, 1976). Copper deficiency may occur, especially in ruminants, when the intake of molybdenum is excessive. A decrease in blood copper and an increase in the urinary excretion of copper have been reported from an area where people had a high intake of molybdenum via food (Kovalskii et al., 1961).

In infants gastrointestinal disturbances may cause copper deficiency.

Excessive intakes of copper have been shown to cause a variety of toxic effects in several animal experiments. Excessive exposure to copper has been shown to cause reversible effects in humans. Such effects have been reported after industrial exposure to fumes - metal-fume fever - and after ingestion of large amounts of copper compounds.

8.1 Local effects and dose-response relationships

8.1.1 Animals

Some earlier papers by Brodsky (1934) and Goralewski (1939) indicate that copper compounds may cause lung changes. Pimentel and Marquus (1969) exposed guinea pigs to Bordeaux mixture (1-2% solution of copper sulfate neutralized with hydrated lime). The exposure lasted six months but the dose cannot be established from the data given. Four of six exposed animals showed micronodular lesions upon X-ray examination and upon microscopical examination of the lungs. In some animals, killed three months after cessation of the exposure, X-ray examination showed regressions of the lesions but microscopical examination revealed that changes were still present.

8.1.2 Humans

Industrial exposure to copper dust or fumes may cause some acute irritation in the upper respiratory tract. Certain investigators have sought to find out whether exposure to copper dust or fumes in industry had given rise to chronic lung damage but their reports have been negative (Gleason, 1968; Hamilton and Hardy, 1974; Cohen, 1974). From Portugal, Pimentel and Marques (1969) and Villar (1974) have reported 1 and 15 cases, respectively, of the so-called vineyard sprayers'lung, a disease attributed to the inhalation of copper sulfate during spraying vineyards with the Bordeaux mixture.

Macroscopically, greenish-blue patches were seen on the lung surfaces. The histological nodular changes resembled those seen in silicosis, but only copper could be demonstrated. Among the fifteen patients described by Villar the time since the last exposure had varied between 1-43 years. Among these fifteen cases three cases of lung cancer and five cases of tuberculosis were diagnosed. Seven of these patients were smokers.

Acute gastrointestinal disturbances may result from the accidental ingestion of food or beverages contaminated by copper released from copper vessels or from hot water geysers (Nicholas, 1968), or from the intentional ingestion of copper salts in attempted suicide (Chuttani et al., 1965).

Copper sulfate is a powerful emetic and has been used clinically as such in the treatment of intoxications, especially in children. The effective dose in children is 250 mg of copper sulfate, corresponding to 100 mg of copper (Holtzman and Haslam, 1968). In adults, the ingestion of about 1 g of copper sulfate, about 400 mg of copper, induces vomiting. Since systemic effects may be incurred from the absorption of copper, the use of copper sulfate as an emetic has been decreasing during the last years.

8.2 Systemic effects and dose-response relationships

8.2.1 Laboratory and domestic animals

Daily subcutaneous injections of copper sulfate for 60 days to rats in a dose of 0.26 mg of copper resulted in large amounts of copper in the liver, around 1,000 mg/kg wet weight in contrast to 4.7 mg/kg in control animals. The exposed rats also showed reductions in hemoglobin content, red cell counts and hematocrits. The mean survival time among exposed animals was 67 days. Histologically, signs of acute toxicity, both hepatic and renal, were seen (Wiederanders et al., 1968).

Rats and pigs given diets with a high content of copper over a prolonged period of time did not show any major deleterious effects (Johnson and Miller, 1961; Kline et al., 1971). On the contrary rats given 50 mg Cu/kg diet and pigs given up to 250 mg/kg diet gained more weight than usual. Pigs given 500 mg/kg diet did display a reduction in weight gain as well as anemia. In the pigs given 250 mg/kg, liver concentrations of copper were about 20 mg/kg wet weight, as compared to about 4 mg/kg in control pigs. but in pigs given 500 mg/kg the liver concentration of copper was 500 mg/kg wet weight (Kline et al., 1971).

Daily oral doses of 20 mg of copper sulfate per kg body weight to sheep resulted in hemoglysis after nine weeks (Gopinath et al., 1974). In sheep killed before the hemolytic crisis, whole blood copper was of the same magnitude as in controls but in sheep which did undergo hemolysis, the copper concentration in blood showed a sharp increase. Liver concentrations in controls were around 50 mg/kg wet weight compared to more than 500 mg/kg in both prehemolytic and hemolytic animals. Hemolysis also caused acute tubular renal damage in the sheep. In an experiment on cows one group was given about 4 mg/kg diet and another about 10 mg/kg diet. No difference appeared in growth, reproduction or milk production but liver levels were about twice as high in animals given the higher copper content (Engel et al., 1964). In ruminants relatively low copper levels in the diet, less than 16 mg/kg, may cause toxic effects if the molybdenum content of the food is low, while a high level of molybdenum in the diet may cause copper deficiency.

8.2.2 Humans

Industrial exposure to copper dust or fumes has been common, but health surveys of workers engaged in the processing of copper have not revealed any signs of chronic disease (Cohen, 1974; Hardy and Hamilton, 1974). Copper fumes and fine dust may cause so-called metal-fume fever (Friberg and Thrysin, 1947; Gleason, 1968). Metal-fume fever is an influenza-like syndrome in which the symptoms disappear after 24 hours (see also the chapter on zinc). Gleason (1968) reported that metal-fume fever appeared after exposure to about 0.1 mg/m^3 of fine copper dust. In two autopsied cases of the so-called "vineyard sprayers'lung" hepatic granulomas were found and copper deposits could be demonstrated histochemically (Pimentel and Menezes, 1975). Liver function tests had indicated liver dysfunction when these patients were alive, but since they were suffering from very severe pulmonary disease, it is not clear how well the copper deposits in the liver were related to the function tests.

After suicidal ingestion of large amounts of copper sulfate, jaundice and renal damage have been seen at average copper concentrations in blood of about 8 mg/l, whereas at a copper level of about 3 mg/l only gastrointestinal disturbances were seen.Of 48 patients who were estimated to have ingested from 1 to 100 g of copper sulfate, 9 died (Chuttani et al., 1965).

A child in whom copper sulfate crystals were applied therapeutically to severely burned skin seven times during nine weeks developed severe anemia. After the last treatment, a hemolytic crisis with icterus took place (Holtzman et al., 1966). High levels of copper in serum and urine, 5.4 mg/l and 2.2 mg/l, indicated that absorption of copper from the wound dressings was responsible. A transient elevation of serum glutamic oxaloacetic transaminase was observed indicating slight liver damage. Recovery was rapid after treatment, which included oral administration of penicillamine. Excessive weight loss and diarrhea were reported in a child given drinks and food prepared from water from a copper-contaminated hot water tap over an extended period of time (Salmon and Wright, 1971). Blood levels of copper were elevated and liver function tests showed pathological development. After removal of exposure plus treatment, recovery was rapid. Biopsy of the liver at a later time showed no pathological signs.

Several reports have emurged on the effects of copper released from dialysis equipment used in the treatment of patients with renal disease. An uptake of copper in the plasma has occuired, resulting in hemolytic anemia. In some cases the reactions have been so severe as to cause death (Ivanovich et al., 1969).

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GERMANIUM

V.B. Vouk

1. Abstract

Animal experiments show that germanium compounds, both inorganic and organic, are rapidly and almost completely absorbed from the lungs and the gastrointestinal tract. The distribution among the organs and tissues is fairly uniform and there is no evidence of preferential uptake or accumulation. Absorbed germanium is rapidly excreted mainly in urine. Data on biological half-times are inadequate.

There is no evidence that germanium is essential either for man or animals.

Germanium tetrachloride is a strong irritant of the respiratory system, skin and the eye, possibly because of easy hydrolysis producing HCl. High inhalation exposures produced in mice necrosis of the tracheal mucosa, bronchitis and interstitial pneumonia. Systemic toxicity of germanium compounds is comparatively low. There seems to be no specific target organs, but the kidney and the liver are usually affected. Trialkylgermanium compounds are less toxic than the corresponding lead or tin alkyls. Germanium compounds do not seem to be carcinogenic. Dimethylgermanium oxide is teratogenic in chickens, but sodium germanate did not produce malformations in hamsters.

There is no information on the toxicity of germanium for man, except some showing that germanium tetrachloride may produce skin irritation.

Inhalation is the main route of exposure under occupational conditions; the main source of germanium for the general population is food.

Short reviews of the toxicology of germanium have been published by Browning (1969), Underwood (1971) and Mogilevskaya (1973).

2. Physical and chemical properties

Germanium, Ge; atomic weight 72.6; atomic number 32; density 5.3 (25°C); melting point 937.4°C; boiling point 2830°C; crystalline form grey-white, brittle solid; oxidation state 2,4. It belongs to the IVb group of the periodic system together with carbon, silicon, tin and lead. Germanium has both metallic and non-metallic properties. It is a n- or p-type semiconductor depending on the impurities present. Of industrial and toxicological interest are elemental germanium; germanium dioxide; sodium germanate; germanium tetrahydride (germane); and germanium tetrachloride. There is a large number of organogermanium compounds, including alkylgermanes and hexaalkyldigermanium oxides.

3. Methods and problems of analysis

Atomic absorption spectroscopy, emission spectrography and spectrophotometry with phenylfluorone are the most widely used methods for the analyses of germanium in environmental and biological samples. The limit of detection of AAS is of the order of 1.5 mg/l and can be reduced to 0.015 mg/l by using a graphite tube atomizer (Amos and Willis, 1966; Johnson and West, 1973). To reduce losses from volatility of germanium, biological samples are ashed at low temperature. Interference of other elements can be eliminated by carbon tetrachloride extraction. Samples are treated in the same way for the analysis by spectrophotometry with phenylfluorone, whose limit of detection is about 0.1-0.5 mg/l (Luke and Campbell, 1956). The achievable precision of the spectrophotometric method is 5-10% (relative standard deviation) (Schroeder and Balassa, 1967a). There is not enough information to evaluate the accuracy of these methods. The limit of detection of emission spectrography (biological samples) is about 1 μg (Geldmacher v. Mallinckrodt and Pooth, 1969) and of the spark source mass spectrometry (SSMS) (in human tissue samples) 0.007 mg/kg wet weight (Hamilton et al., 1972/1973).

4. Production and uses

4.1 Production

Some silver and zinc ores contain considerable amounts of germanium but there is no widely occurring germanium ore. The total estimated world production of germanium is of the order of 100 tons annually, the largest producers being South Africa and Zaire; it is primarily linked with zinc mining. Germanium can also be recovered from waste products of coal and coke technology. Germanium tetrachloride is an intermediate in technological processes for the preparation of germanium dioxide and organogermanium compounds.

4.2 Uses

The high purity elemental germanium is used primarily in semiconductor devices such as transistors, diodes and rectifiers (90% of total consumption). Other uses include the manufacture of specialized optical glasses and infra-red equipment.

5. Environmental levels and exposures

5.1 General environment

5.1.1 Food

A spectrophotometric method using phenylfluorone revealed the presence of germanium in all food items analysed (Schroeder and Balassa, 1967a). However, only 5 items had more than 2 mg Ge/kg (raw clams, canned tuna, dried panfish, canned baked beans and tomato juice) and 15 more than 1 mg Ge/kg. Selected hospital diets contained on the average 0.88 mg Ge/kg wet weight. The daily intake of germanium may vary from 400 to 3500 µg (Schroeder and Balassa, 1967a). Hamilton and Minski's (1972/1973) estimate of the mean daily intake in the United Kingdom is 367±159 µg (spark source mass spectrometry).

5.1.2 Water, soil and rocks, ambient air

Durum and Haffty (1961) did not find germanium in 59 water samples from 15 major rivers in the United States and Canada (spectrophic method).

Some soils in the United States were found to contain 0.6-1.3 mg Ge/kg (Schroeder and Balassa, 1967a) which is of the same order of magnitude as the abundance of germanium in the earth's crust (1.5 mg/kg) (Fyfe, 1974).

Considerable amounts of germanium are discharged into the atmosphere by coal combustion. Puone (1970) estimated 2000 tons per year as the amount discharged in stack gases, flue dust and ashes from coal burning plants in the United Kingdom. Coal ash may contain 20-280 mg Ge/kg (Coal Research Section, 1972). Concentrations of germanium in urban air have not been reported.

5.2 Working environment

Exposure to germanium tetrachloride and its hydrolysis products (GeO_2, HCl) may occur in the production of germanium and its compounds. Dust concentrations ranging from 5 to 70 mg/m^3 (corresponding to germanium concentrations of about 7 mg/m^3) have been reported to occur in the production of germanium monocrystals. In some cases they contained up to 30% of free silica (Gel'dman, 1960; Mogilevskaja, 1973).

6. Metabolism

6.1 Absorption

6.1.1 Inhalation

The rate of clearance of deposited elemental germanium particles (mean size 1.4 µm) from the lungs of rats is exponential (52% in 24 hours, 18% remaining 7 days after exposure). Radiochemical examination of the tissues showed that part of the material enters the circulation and reappears in the kidney and liver one hour after exposure. The clearance of germanium dioxide particles (mean size 0.4 /um) was even more rapid (79% within 24 hours)(Dudley, 1953).

6.1.2 Ingestion

Neutralized germanium dioxide is rapidly absorbed after stomach intubation to rats (73.4% in 4 hours; 96.4% in 8 hours) (Rosenfeld, 1954). Equally rapid absorption of tetraethylgermanium from the gastrointestinal tract of mice was demonstrated by Caujolle et al. (1963). Schroeder and Balassa (1967a) found that the concentrations of germanium in human urine were about the same as the concentrations in the diet, indicating that dietary germanium is well absorbed.

6.2 Distribution

Absorbed germanium is distributed fairly uniformly between erythrocytes and plasma (2:3 ratio) and is not bound to plasma proteins (Rosenfeld, 1954). There is no preferential localization of germanium in soft tissues although in exposed rabbits and dogs (i.v. injection of GeO_2) the highest concentrations were found in the kidney, liver, spleen, gastrointestinal tract and bone (Dudley and Wallace, 1952). Schroeder and Balassa (1967b) and Schroeder et al. (1968) kept mice and rats for life on normal laboratory diet (0.33 mg Ge/kg) and drinking water containing 5 mg Ge/l as sodium germanate. Germanium was widely distributed in the body and there was no selective retention or storage. Essentially the same distribution was found in mice following ingestion of tetraethylgermanium (Caujolle et al., 1963).

6.3 Excretion

Absorbed germanium is preferentially excreted in urine both in man (Schroeder and Balassa, 1967a) and in animals. In rats, 64.8% of an i.p. dose of sodium germanate (100 mg/kg) was excreted in urine and 4.7% in feces within 1 day, the total excretion in 5 days amounting to 78.8 and 13%, respectively (Rosenfeld, 1954). Excretion of germanium by rabbits following i.v. injection of GeO_2 amounted to 72% of the dose in urine, and 9% in feces within 72 hours. In dogs, 90% of an injected

GeO_2 dose was excreted in urine within 72 hours (Dudley and Wallace, 1952).

6.4 Biological half-time

Using a simple exponential model and Rosenfeld's 1954 data for rats biological half-times can be roughly estimated as 1 1/2 days for the whole body retention, 2 days for liver and 4.5 days for the kidney. The corresponding values for man as used by ICRP (1960) are whole body retention 1 day; liver 7.5 days; kidney 12 days. The agreement is not too good, except for the whole body retention.

7. Normal levels in tissues and biological fluids

There is little information on the "normal" values of germanium in human tissues and fluids. Hamilton et al. (1972/1973) published the following preliminary values for some human tissues in the United Kingdom (mean concentrations, mg/kg wet weight, spark source mass spectrometry): Lymph node 0.0009; muscle 0.003; liver 0.04; lung 0.09; brain 0.1; blood 0.2; testes 0.5; and kidney 9.0. The concentrations of germanium in human lung tissue (SSMS, 247 samples) as reported by Brown and Taylor (1975) range from 0.08-12 mg/kg dry weight. Schroeder and Balassa (1967a) found 0.29 mg/l in serum, 0.65 mg/l in erythrocytes and 1.26 mg/l in urine (spectrophotometry with phenylfluorone).

8. Effects and dose-response relationships

8.1 Inorganic compounds

8.1.1 Local effects and dose-response relationships

8.1.1.1 Animals

Seven months after an intratracheal administration of 30, 50 and 70 mg of germanium dioxide, rats showed thickening of alveolar walls and hyperphasia of pulmonary lymphatic vessels (Mogilevskaja, 1973). Changes in the respiratory system following single (1.4-40 g/m^3, 2 hours) and repeated

(500-700 mg/m^3, 2 hours/day, 40 days) inhalation exposure of mice to germanium tetrachloride were dose related and ranged from irritation of the respiratory system to necrosis of the tracheal epithelium, catarrhal desquamative bronchitis and interstitial pneumonia (Kal'sada, 1964). No respiratory changes were reported as resulting from long-term (3, 4, 5 and 7 mg/m^3, calculated as HCl, 7 months) inhalation exposure of rats to germanium tetrachloride (Kurlajandski) et al., 1968). No local respiratory effects were reported following inhalation of germanium tetrahydride either in acute or chronic experiments (Gus'kova, 1974). Neutralised germanium dioxide (topical application, 2 times/day, two weeks) induced no irritation of the shaved skin of the rat (Rosenfeld, 1954). Ulceration and necrosis of the skin were observed in rabbits following two-hour exposure to germanium tetrachloride. The effects observed in guinea pigs and rats were much milder (Kal'sada, 1964; Kurlajandski et al., 1968).

Germanium tetrachloride has a pronounced irritating action on the conjunctivae of the eye in rats, rabbits and mice (Kal'sada, 1964; Kurlajandski et al., 1968).

Local effects of germanium chloride are very likely due to a combined action of the compound and its hydrolysis products (GeO_2, HCl, Ge_2Cl_6, etc.) (Kurlajandski et al., 1968).

8.1.1.2 Humans

There is no information on local effects of germanium compounds in the respiratory system. Mild irritation of the skin is produced by germanium tetrachloride (Kal'sada, 1964).

8.1.2 Systemic effects and dose-response relationships

8.1.2.1 Animals

Inorganic germanium compounds seem to have a comparatively low systemic toxicity. An exception is germanium tetrahydride.

Eight weekly i.p. doses of neutralised germanium dioxide did not inhibit the growth of rats but the ingestion of the same compound in food (1000 mg/kg) or drinking water (100 mg/l) inhibited the growth of young rats and caused a mortality of 50% in four weeks. The survivors seemed to recover after that although they continued to ingest about the same dose for another 8 weeks (Rosenfeld and Wallace, 1953).

Lethal doses of germanium dioxide appear to induce a severe hypothermic shock in rats, and rectal temperatures of 26.7°C were frequently observed (Rosenfeld and Wallace, 1953).

8.1.2.1.1 Liver

Degenerative changes and necrosis, sometimes associated with functional impairment (e.g. reduced detoxifying capacity - hippuric acid test) were observed in acute, subacute and chronic studies by Kal'sada, 1964 (mice; $GeCl_4$ inhalation, 1.7-40 g/m^3, single exposures; and 500-700 mg/m^3, 2 hours/day, 40 days), Kurlajandskij et al., 1968 (rats; $GeCl_4$ inhalation, 300-700 mg/m^3, 7 months); and Gus'kova, 1974 (rats and guinea pigs; GeH_4 inhalation, 260-1400 mg/m^3, single exposures). Increased incidence, compared to controls, of fatty degeneration of the liver was found in rats following lifetime exposure to 5 mg Ge/l as sodium germanate in drinking water (Schroeder et al., 1968) but there was no effect in a similar experiment with mice (Schroeder and Balassa, 1967b).

8.1.2.1.2 Kidney

Degenerative changes in the epithelium of the proximal tubules were noted by Kal'sada (1964), Kurlajandskij et al. (1968) and Gus'kova (1974) following high level inhalation exposures to germanium tetrachloride and germanium hydride, respectively. The same morphological changes accompanied by proteinuria had higher incidence in rats exposed to sodium germanate than in the controls (Schroeder et al., 1968). For exposure condition and animal species used see 8.2.1.1).

8.1.2.1.3 Hematological effects

Early work on biological effects of germanium compounds indicated an erythropoietic stimulation produced by subcutaneous injection of germanium dioxide and sodium germanate but this could not be confirmed by Bailey et al. (1925) (rabbits, germanium dioxide, repeated i.p. injection, 7 weeks, total doses 28-280 mg/kg) and Rochow and Sindler, 1950 (rabbits and hamsters, dimethylgermanium oxide, single and repeated s.c. doses up to 1 g Ge/kg). Similarly, multiple i.p. doses of sodium germanate (100 mg/kg) and repeated oral doses of neutralized GeO_2 (0.9-170 mg/kg body weight) had no hematological effects in rats (Rosenfeld and Wallace, 1953). Some changes in the blood picture, of uncertain biological significance, such as increased hemoglobin, increased number of erythrocytes and leukocytes, were observed by Kurlajandskij et al. (1968) (rats, $GeCl_4$ inhalation, 300-700 mg/m^3, 7 months) and Gus'kova (1974) (rats and guinea pigs, GeH_4 inhalation, 50-250 mg/m^3, 4 months).

8.1.2.1.4 Nervous system

Lethal exposures of rats to germanium dioxide (600-1200 mg/kg, single i.p. dose, Rosenfeld and Wallace, 1953), of mice to germanium tetrachloride (20-40 g/m^3, Kal'sada, 1974) and germanium hydride (2 g/m^3, Gus'kova, 1974) were accompanied by various neurological signs (excitation, impairment of locomotor activity, listlessness, hypothermia and convulsions). Histochemical changes in the brain observed in rats by Kurlajandskij et al. (1968) following chronic inhalation exposure to germanium tetrachloride (3-7 mg/m^3, 7 months) are difficult to interpret.

8.1.2.2 Humans

There are no data on the systemic toxicity of germanium compounds in man, and no reports on occupational medicine experience.

8.2 Organic compounds

The toxicity of several trialkylgermanium compounds was studied by Cremer and Aldridge (1964). Triethylgermanium acetate was toxic to rats in intravenous doses of 50 mg/kg body weight, and orally at 250 mg/kg. Tri-n-butylgermanium was tolerated orally in single doses up to 375 mg/kg. Trialkylgermanium compounds had less than one-tenth the toxicity of triethyltin or triethyllead and did not appear to have a predominant effect on the central nervous system. Among the tetraalkylgermanium compounds evaluated by Caujolle et al. (1966) the least toxic were those with saturated normal symmetric radicals. The ramification and halogenation of organic radicals increased the biological activity. Higher hexaalkyldigermanium oxides (butyl, amyl, hexyl) were less toxic than the ethyl homologue (Bouisson et al., 1964).

8.3 Carcinogenicity, teratogenicity and mutagenicity

Studies of Kanisawa and Schroeder (1967) on mice and of Schroeder et al. (1968) on rats (lifetime exposure to 5 mg Ge/l drinking water as sodium germanate) did not produce any evidence on the carcinogenicity of germanium compounds.

Dimethylgermanium oxide, an analog of acetone, was shown to produce a variety of malformations in chick embryos at 72 and 96 hours of incubation, ED_{50} being 1.8 and 2.5 mg/embryo, respectively, as compared to 17.9 and 25.1 for acetone (Caujolle et al., 1965). Ferm and Carpenter did not find any teratogenic or fetotoxic effect in hamsters treated with sodium germanate (40-100 mg/kg, i.v. injection, 8 days gestation).

There is no information on the mutagenicity of germanium compounds.

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INDIUM

Bruce A. Fowler

1. Abstract

Indium compounds are poorly absorbed following ingestion but moderately taken up after inhalation exposure. Muscle, skin, and bone constitute the main body storage sites. Ionic indium is excreted primarily in the urine while fecal elimination is the predominant route for removal of colloidal indium compounds from the body. A biphasic pattern of excretion and a whole-body biological half-time on the order of two weeks have been reported for both chemical forms.

Ionic indium compounds are concentrated by the kidneys, producing renal failure, while colloidal indium is taken up by organs of the reticuloendothelial system, causing damage to the liver and spleen.

Indium is a non-essential element.

2. Physical and chemical properties

Indium, In, atomic weight 114.8; atomic number 49; density 7.3; melting point 156.6°C; boiling point 2,080°C; crystalline form soft silver-white metal, tetragonal; oxidation state 1,2,3. More than 30 inorganic forms of indium are known. Indium trichloride, indium oxide, indium sulfate, indium sulfide, indium sesquioxide, and colloidal indium hydroxide are the ones to be dealt with here.

3. Methods and problems of analysis

A spectrochemical method for determining indium in biological materials has been reported by Kinser et al. (1966). The detection limit for indium by this method is 0.002 µg indium with a standard deviation of approximately 10-15 percent. Neutron activation has been used to analyse for indium in rocks (Rey et al., 1970) and seawater (Matthews and Riley, 1970). The detection limit for indium in seawater is 0.006 µg/l and the coefficient of variation is about 5 percent (Matthews and Riley, 1970).

Polarography has been reported to permit indium analysis in water with a detection limit of 1 µg/l and a precision of about 1 percent (Maienthal and Taylor, 1968).

4. Production and uses

4.1 Production

Indium is recovered as a by-product of zinc smelting. Acid leaching of indium from crude zinc liquors with its subsequent precipitation as a phosphate or acid leaching followed by precipitation on metallic zinc rods are two widely used methods (Stokinger, 1966).

Production figures for indium in the United States are not available. In 1970 the United States imported 401,028 troy ounces of indium (Minerals Yearbook, 1972).

4.2 Uses

The more important uses of indium include its incorporation into solders, alloys, semiconductors, and automobile bearings as a hardening agent which improves resistance to corrosion. Indium oxide is used as a coloring glass while indium sulfide is used in electroplating. Radioisotopes of indium in compounds such as indium trichloride and colloidal indium hydroxide are used in the treatment of tumors and organ scanning (Stern et al., 1966; 1967; Hart and Adamson, 1971). Indium has been used in the past to strengthen solders, dental alloys, and as an electroplating agent.

5. Environmental levels and exposures

5.1 Food

There have been no published reports on indium concentrations in foodstuffs.

5.2 Water, soil, and ambient air

Indium concentrations in sea water have been found to average less than 20 μg/l (Goldberg, 1965). Neutron activation studies (Matthews and Riley, 1970) have reported the concentration of indium in Atlantic Ocean water to be about 0.1 ng/l. This element is also rare in soil as it comprises only about $1 \cdot 10^{-5}$ percent of the earth's crust (Sunderman and Townley, 1960).

Indium concentrations in air and rain in England have been reported to be about 0.3 ng/kg and less than 0.5 μg/l, respectively (Peirson et al., 1973).

6. Metabolism

6.1 Absorption

6.1.1 Inhalation

The absorption of ^{114}In sesquioxide particles by rats following inhalation has been estimated to be between 3-6 percent of the total dose following a single 1 hour treatment and about 18 percent for sequential 1 hour exposures on 4 successive days (Morrow et al., 1958).

6.1.2 Ingestion

The intestinal absorption of indium in rats has been reported to be about 0.5 percent of the administered dose (Smith et al., 1960). No data are currently available for humans.

6.2 Distribution

Ionic indium is transported in the blood bound to transferrin (Hosain et al., 1969; Castronovo and Wagner, 1973) and has been found to be cleared from the blood of mice given an intravenous injection within 3 days (Castronovo, 1970; Castronovo and Wagner, 1971).

Distribution of indium among body viscera is largely determined by chemical form. Ionic indium is extensively accumulated by the kidney while colloidal indium oxide is accumulated by the liver, spleen, and other organs of the reticuloendothelial system. Three days following a single intravenous injection, about 20 percent of a tracer dose and 30 percent of an LD_{100} dose of ionic ^{114}In were found in the kidneys of mice on a per gram of tissue basis. In contrast, mice injected with colloidal ^{114}In concentrated about 64 percent of the tracer dose and 40 percent of the LD$_{100}$ dose in their livers on a per gram of tissue basis after three days (Castronovo, 1970; Castronovo and Wagner, 1971).

6.3 Excretion

The primary route of indium excretion from the body is determined by the chemical form administered. Ionic indium is mainly excreted in the urine while colloidal indium complexes are primarily excreted via the feces. Mice have been found to excrete 52 percent of an administered dose of ionic indium in the urine and 53 percent of a dose of colloidal indium in the feces (Castronovo, 1970; Castronovo and Wagner, 1971; Castronovo and Wagner, 1973).

6.4 Biological half-time

The biological half-time for indium is somewhat dependent upon the chemical form administered and excretion seems to follow a biphasic pattern. Mice given intravenous injection of ^{114}indium chloride showed a biological half-time of 1.9 days for the fast phase component representing about 50 percent of the body burden and 69 days for the slow phase. Hydrated ^{114}indium oxide had a biological half-time of 2 days for the fast phase component representing about 25 percent of the body burden and 73.8 days for the slow phase following intravenous injection (Castronovo, 1970; Castronovo and Wagner, 1971; Castronovo and Wagner, 1973). Stern et al. (1967) found a biological half-time of 3.5 days for clearance of hydrated indium oxide from the lungs of mice following intravenous administration. A whole-body biological half-time of 14-15 days was reported by these authors.

Smith et al. (1960) reported that about 60 percent of an intratracheal injection of radioactive indium left the lungs of rats within 16 days. Excretion of indium from the bodies of these animals was also biphasic. The biological half-time for inhaled ^{114}indium sesquioxide particles with no apparent correction for decay has been found to be about 2-4 days in the rat (Morrow et al., 1958).

7. Normal levels in tissues and biological fluids

There have been no published reports concerning normal tissue concentrations of indium in humans or other species.

8. Effects and dose-response relationships

Indium is considered non-essential.

8.1 Local effects and dose-response relationships

8.1.1 Animals

There have been no published reports concerning local effects in animals.

8.1.2 Humans

Raiciulescu et al. (1972) reported that three patients out of a total of 770 injected with colloidal ^{113}indium for liver scanning developed severe vascular shock within 20 minutes after treatment. Shock was found to last from 10 minutes to 1 hour.

8.2 Systemic effects and dose-response relationships

8.2.1 Animals

The primary toxic effects of ionic indium are exerted on the kidneys while colloidal hydrated indium oxide damages organs of the reticuloendothelial system. Intravenous injection of indium chloride has been reported to cause extensive necrosis of the renal proximal tubules in both rats (3.6 mg/kg) and mice (16.5 mg/kg) (Downs et al., 1959; Castronovo, 1970; Castronovo and Wagner, 1971). Administration of colloidal hydrated indium oxide by this route produced necrosis cells in the liver and spleen (Downs et al., 1959; Stern et al., 1967; Castronovo, 1970; Castronovo and Wagner, 1971). Lung damage has also been reported in mice given subcutaneous injections of $In(SO_4)_3$ (Yoshikawa and Hasegawa, 1971). Decreased hemoglobin and neutrophil counts have been observed in rats, mice and rabbits injected with ionic indium (Steidle, 1933; McCord et al., 1942; Downs et al., 1959; Yoshikawa and Hasegawa, 1971).

Administration of ionic indium at a concentration of 5 mg/l in drinking water has also been reported to cause mild growth depression in mice (Schroeder and Mitchener, 1971).

Implantation of indium-treated silver discs into rabbits has been found to produce only foreign body reactions (Harrold et al., 1943).

8.2.2 Humans

There have been no reported cases of systemic effects in humans exposed to indium.

8.3 Teratogenic, carcinogenic, and genetic effects

Intravenous administration of ionic indium to pregnant hamsters has been reported to produce malformations of the fetal digits at dose levels below 1 mg/kg and embryolethality at higher dose levels of 2-20 mg/kg (Ferm and Carpenter, 1970). There are currently no published studies on the carcinogenic or genetic effects of indium.

8.4 Interactions with ferric dextran, thorotrast, and gelatin

Concomitant administration of ferric dextran to rats and hamsters given intravenous doses of ionic indium has been reported to protect against liver damage and embryopathic effects in these respective species (Gabbiani et al., 1962; Ferm, 1970). Administration of thorotrast and gelatin prevented damage to the reticuloendothelial system by colloidal indium hydroxide (Evdokimoff and Wagner, 1972).

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LEAD

Kenzaburo Tsuchiya

1. Abstract

The rate of deposition, retention and absorption of inhaled lead is highly variable, depending on particle size, physicochemical form of lead and the efficiency of lung clearance mechanisms. There is no evidence of accumulation in the lungs and all lead retained is eventually absorbed or transferred to the gastrointestinal tract. For practical purposes it is assumed that, on average, about 30% of inhaled lead is absorbed.

About 10% of ingested lead is absorbed in the gastrointestinal tract. This fraction may be higher for infants and children.

Lead body burden consists essentially of two compartments: bone (containing about 90% of the total content) with a half-time of about 20 years; the amount of lead in this compartment increases throughout life; and a smaller compartment with a half-time of about 20 days (blood, soft tissue and rapidly exchangeable bone fraction).

Absorbed lead is excreted mainly via urine (about 80%) and gastrointestinal secretion; small amounts are excreted in milk, sweat, hair and nails. Placental transfer of lead has been demonstrated.

There is no evidence that lead is essential for either man or animals.

The most common form of acute lead poisoning is gastrointestinal. Acute lead encephalopathy is rare in adults, more frequent in children. Anemia is a common chronic systemic effect resulting mainly from the effects of lead on heme synthesis. Inhibition of δ-aminolevulinic acid dehydrase (ALA-D) and elevation of protoporphyrin in erythrocytes are the earliest effects followed

by increase in urinary δ-aminolevulinic acid (ALA) and coproporphyrin excretion, and fall in hemoglobin level. These effects are associated with increasing blood lead levels, inhibition of ALA-D starting at 20-30 μg/100 ml; increased ALA excretion occurs at blood lead levels of about 40-50 μg/100 ml. Chronic encephalopathy may result from prolonged lead absorption but it may also be a residual effect of acute encephalopathy. Peripheral neuropathy is now rare, although sub-clinical effects such as reduced nerve conduction can be detected at lead blood levels of about 50 μg/100 ml. Lead colic may occur at comparatively low levels of exposure and is usually accompanied by other symptoms and signs. Renal effects are mostly reversible but long-term exposure associated with blood lead levels of 70-80 μg/100 ml may cause irreversible functional and morphological changes. There is no conclusive evidence that lead can damage liver, cardiovascular system or reproductive function. Lead compounds are not considered as carcinogenic to man. Factors that can modify the effects of lead include age, diet and possibly cadmium and zinc.

Accidental or occupational exposure to alkyllead compounds may result in acute encephalopathy which is different from the effects of inorganic lead compounds on the central nervous system.

For differential diagnosis of lead it is essential to determine lead in blood, and ALA and coproporphyrin in urine. CaEDTA is the most widely and effectively used therapeutic agent. If over-exposure is detected early, prognosis is good.

Primary route of exposure for the general population is food, for occupational groups inhalation; important sources of exposure for children in some countries are lead paint, and soil and dust. Estimated daily intake via food is for adults about 200-300 μg; air pollution may contribute up to about 20 and drinking water less than 20 μg. Estimated daily absorption from all sources is up to 30 to 40 μg.

Comprehensive reviews and symposia on lead toxicology have been published by NAS (1972), CEC (1972), Associate Committee on Scientific Criteria for Environmental Quality (1973), Goyer and Rhyne (1973), Interdepartmental Working Group on Heavy Metals (1974), Task Group on Metal Toxicity (1976) and WHO (1976).

2. Physical and chemical properties

Lead, Pb, periodic system group IVB; atomic weight 207.19; atomic number 82; density 11.34; melting point 327.5°C; boiling point 1740°C; crystalline form silver-bluish white soft metal, cubic; oxidation states 0, + 2 and + 4.

In most inorganic compounds, lead is in the oxidation state +2. The salts of lead (II), lead oxides and lead sulfide are poorly soluble in water, with the exception of lead acetate, lead chlorate and, to some extent, lead chloride.

Tetramethyllead and tetraethyllead are the most important organolead compounds because of their widespread use as anti-knock fuel additives. Both are colorless liquids with boiling points of 110°C and 200°C, respectively. At these temperatures, or slightly below, they begin to decompose.

3. Methods and problems of analysis

A major source of errors in the determination of lead in environmental samples is the secondary contamination during sampling or analysis, particularly of food and biological media.

Both high and low volume samplers can be used in air sampling for lead. The pore size of filters should be less than 0.2 µm (Lee and Goranson, 1972). For sampling of organolead compounds both liquid scrubbers with iodine monochloride and solid scrubbers with activated carbon, cristobalite or iodine crystals are used (Purdue et al. 1973; Harrison et al., 1974).

For most purposes water samples may be analyzed for lead without separating suspended material from the liquid phase.

Soil and dust samples are first dried, then homogenised by grinding and sieving (Thornton and Webb, 1975)

Pekkarinen (1970) has reviewed the advantages and limitations of the two main methods for the studies of lead in food: the duplicate portion technique and the equivalent composite technique. The first method, used by Kehoe (1961) for the daily determination of lead intake over long periods, involves the analysis of duplicates of meals actually consumed, and thus defines the variability of intake; it is expensive and time consuming. The equivalent composite technique is based on the analysis of formulated meals typical for given populations; the main problem is the representativeness of such formulations.

Special precautions are needed to avoid secondary contamination of blood and other tissue and body fluids samples. These include the use of lead-free silicate glass, glass cleaning with mineral acids and deionized water, use of polypropylene syringes and stainless steel needles (NAS, 1972). Even more stringent precautions should be taken when lead is determined in micro-samples of blood (Mitchell et al., 1974).

Most analytical methods used for routine determination of lead require sample pretreatment. Dry as well as wet ashing is used to destroy organic matter; low temperature ashing can also be used for small samples of biological material.

The dithizone method based on spectrophotometric determination of a red complex that lead forms with diphenylthiocarbazone is still widely used (NAS, 1972), although it is being gradually displaced by atomic absorption spectrophotometry.

The conventional AAS requires pretreatment of biological samples by dry or wet ashing. More recently various "flameless" AAS procedures have been developed in which the sample is heated and ashed in the receptacle of the AAS instrument (Cernik, 1974). In addition, the sample size for blood can be reduced from the milliliter to the microliter range without increasing the limit of detection which is for the flame AAS of the order of 0.01 mg/l and for the flameless AAS (graphite atomization) about $1 \cdot 10^{-5}$ mg/l (Christian and Feldman, 1971; Slavin et al., 1972). The achievable precision of AAS methods is of the order of 7-9% (relative standard deviation, lead in blood; Evenson and Pendergast, 1974).

Electroanalytical methods are also useful, particularly polarography and anodic stripping voltametry (ASV). Neutron activation analysis is not likely to find wide application for lead analysis in the near future, because of the need of a fast neutron source. Another non-destructive method with good potential for specialized applications is X-ray fluorescence (Kneip and Lauren, 1972; Rasberry, 1973).

Matson et al. (1971) reported good agreement of results obtained by the dithizone method, AAS and ASV but the experience of the present author showed that more practice and better trained analysts are required to obtain reliable results by ASV than by AAS. Normal levels of lead in blood (10-20 µg/100 ml) can be easily determined in a 5 ml sample by AAS; only 0.2 ml is required for ASV; one drop is sufficient for the flameless AAS (Delves, 1970).

In spite of comparatively long experience with the analysis of lead in blood, the concentrations are often not determined precisely and accurately. In a recent interlaboratory comparison among 66 European laboratories, the results differed by a factor up to 10 or more (Berlin et al., 1976).

A very thorough training of the analysts and frequent checks with standard samples are therefore strongly recommended. In addition, great care is needed in the ashing of the samples.

4. Production and uses

4.1 Production

The most important lead minerals are galena (lead sulfide), cerrusite (lead carbonate) and anglesite (lead sulfate). Galena occurs mostly in deposits which also contain zinc minerals and small amounts of copper, iron and a variety of trace elements.

Mixed lead and zinc ores account for about 70% of total primary lead production.

The most important lead mining countries are the United States, the USSR, Australia, Canada, Peru, Mexico, China, Yugoslavia and Bulgaria, accounting for about 70% of the world mine production in 1975 which amounted to 3.6 million tons as compared to 2.6 million tons in 1965 (International Lead and Zinc Study Group, 1976).

Lead is also produced from scrap (secondary lead) which accounts for about 35% of the total world lead supply (Federal Institute for Minerals Research and German Institute for Economic Research, 1972). Total current lead production (primary and secondary) amounts to about 5 million tons.

Lead production from a sulfide ore (3-8% Pb) includes concentration (to 55-70% Pb), sintering in which lead is oxidized, reduction of lead oxide and refining to eliminate impurities.

4.2 Uses

The largest consumer of lead in 1974 was the storage battery industry (40%) followed by alkyllead production (12%), cable sheathing (9.2%),pigments (12%), alloys (10.8%) and various semimanufacturers (12%). In absolute amounts the world consumption of lead in 1975 was about 4.1 million tons, more than 50% of which was used by the automobile industry (mainly batteries and alkyllead). In 1973 the manufacture of alkyllead consumed about 380,000 tons of refined lead (International Lead and Zinc Group, 1976).

5. Environmental levels and exposures

5.1 General environment

5.1.1 Food

Lead concentrations in food products range from undetectable levels to a few mg/kg wet weight (Waldron and Stöfen, 1974). Horiguchi (1974) compared lead concentrations in various food products in Japan in 1970 with those reported for 1950 (Horiuchi et al., 1956). No major differences were found, although two different analytical methods were used (dithizone and AAS with wet ashing, respectively). The values reported by Schroeder et al. (1961) may serve as an example of lead concentrations in food: condiments contained about 1 mg/kg; fish and seafood 0.2-2.5 mg/kg; meat and eggs 0.2-0.4 mg/kg; and grains and vegetables up to 1.4 mg/kg. The concentrations of lead in milk are of particular concern, milk being the main dietary constituent for infants. Human breast milk contains lead in concentrations of about 5-12 µg/l (Lamm and Rosen, 1974; Murthy and Rhea, 1971). Unprocessed cow's milk has a similar concentration. Processing may considerably influence the lead content. Whole bulk milk was found to have about 40 µg/l in contrast to 200 µg/l in milk that had been processed by evaporation (Mitchell and Aldous, (1974).

5.1.2 Water

Lazarus et al. (1970) measured lead concentration in rainwater in 32 US stations; the mean was 34 µg/l and the maximum value observed 300 µg/l. The mean concentration of lead in rainwater in Yokohama, Japan ranged from 8 µg/l in residential areas to about 30 µg/l in business areas (Kobayashi, 1972). In the areas of heavy traffic, lead in rain may exceed 100 µg/l and reaches 500 µg/l (Ettinger, 1966).

Since 1962, lead concentrations in water supplies in the USA have generally not exceeded 50 µg/l, the US Public Health Service standard (NAS, 1972). This is supported by Durfor and Becker (1964) who found that lead in water supplies in about 100 large American cities ranged from traces to about 60 µg/l. However, when lead pipes or tanks are used and the water is soft, lead concentrations may be so high (up to 3000 µg/l, Goldberg, 1974) as to cause lead poisoning (Beattie et al., 1972). Plastic pipes containing lead stearate may also contaminate drinking water (WHO, 1976).

Surface water usually contains lead in concentrations below 100 µg/l (Kopp and Kroner, 1975) and in unpolluted areas in the range of about 1 µg/l (Zukovickaja et al., 1966).

A recent survey of the rivers in the Midi-Pyreneus region, France, showed mean dissolved lead concentrations of about 7 to 10 µg/l (Servant, 1973). Lead concentration in deep ocean waters is about 0.01-0.02 µg/l but in surface ocean water 0.3 µg/l (Chow and Patterson, 1966).

5.1.3 Soil and plants

The natural concentration of lead in soil is in the range of 2 to 200 mg/kg (NAS, 1972) with mean values of about 16 mg/kg, but the variation from one location to another is considerable (Waldron and Stöfen, 1974). The concentration of lead in street dust and surface soil may be sometimes extremely high and may represent a hazard to children. For example, the mean lead concentration in street dust from residential and commercial areas in 77 Mid-western cities in the USA amounted to about 1600 to 2400 mg/kg (NAS, 1972) and Kennedy (1960) reported that lead in soil near a lead mining area in Idaho reached 20,000 mg/kg.

Grass samples may show high lead concentrations near the roads with heavy traffic, the mean values ranging from about 250 mg/kg at the roadside to about 160 mg/kg at a distance of 25 m (NAS, 1972). This is mostly due to external contamination, because the uptake of lead by plants from soil does not seem to be much influenced by the concentration of lead in soil (Ter Haar, 1970).

5.1.4 Ambient air

The lead concentrations in ambient air of large cities range from about 0.02 µg/m^3 to about 10 µg/m^3 (means of 24-hour samples) (Tepper and Levin, 1975; Tsuchiya et al., 1975; Waldron and Stöfen, 1974). These figures do not necessarily indicate the exposure throughout the entire year and the sampling sites were not all at the same distance from the ground. A good picture of lead concentration in ambient air is obtained from the data collected in 1971-1972 in some European cities as shown in Table 1. In contrast the lead concentrations in air above the North Central Pacific Ocean and South Indian Ocean are of the order of 0.001 µg/m^3 (Chow and Bennet, 1969; Egorov et al., 1970).

5.1.5 Special exposures

The concentration of lead in illicitly distilled whiskey may be above 1 mg/l, and cause chronic poisoning (Patterson and Jernigan, 1969; Whitfield et al., 1972). Wine is another possible source of lead intake for some people, the average concentrations ranging from 130-190 μg/l (Boudéne et al., 1975).

Improper glazing of earthenware vessels results in leaching of lead, particularly if they contain acidic liquids. Cases of poisoning from this source were reported, for example, from Yugoslavia (Beritic and Stahuljak, 1961) and the United Kingdom (Whitehead and Prior, 1960) and more recently from the USA (Klein et al., 1970).

Lead based paints represent an important source of excessive lead intake in children (Chisholm and Harrison, 1956). A recent study revealed that 80% of children examined because of excessive lead absorption had pica (Sachs, 1974). Guinee (1973) reported that in children with blood lead concentrations equal or greater than 60 μg/100 ml, 75% lived in homes with at least one lead painted surface, but the high blood lead levels found in children are not always easily explicable in this way (Greenfield et al., 1973). High concentrations of lead in soil in the vicinity of some houses may be another source of lead intake, related either to the weathering of lead-based paint or to the accumulation of lead from automobile exhausts (Ter Haar and Aronow, 1974; WHO, 1976). Children may also be exposed to lead from colored newsprint (Hankin et al., 1973), or lead-painted toys.

Lead content in tobacco may vary from about 3 μg (Szadkowski et al., 1969) to 12 μg per cigarette of which about 2% is transferred to the mainstream smoke (Petering and Menden, 1976), resulting in an inhalation of about 1.2 to 4.8 μg lead per 20 cigarettes.

5.2 Working environment

Lead smelting and refining is probably the most hazardous operation with respect to exposure to lead. Mean concentrations of lead in air may reach 80-4000 µg/m^3 (WHO, 1976). Tola (1974) has recently reported on lead exposure in the secondary lead smelters in Finland; 16 out of 20 workers examined had lead blood levels exceeding 70 µg/100 ml.

Oxide mixing appears to be the most hazardous operation in the storage battery production with recorded mean concentrations of lead in air up to 2000 µg/m^3 (Tsuchiya and Harashima, 1965). Although these values may not be representative, they illustrate the problem. Other occupations with possible lead exposure include shipbreaking and welding (Rieke, 1969), printing (Tsuchiya and Harashima, 1965), alkyllead manufacture (Linch et al., 1970), plastics production (HM Chief Inspector of Factories, 1973) and rubber tire industry (Sakurai et al., 1974). For additional information reference is made to Kernberg (1973).

5.3 Estimates of total intake

When averaged over several months the concentration of lead in urban air would rarely exceed 1 µg/m^3; assuming that, on the average, 20 m^3 of air is inhaled per day, the upper limit for the inhalation intake would be about 20 µg, but a more realistic estimate would be about 10-15 µg per day.

Lead intake through drinking water would generally not exceed 50 µg per day. The mean intake would be closer to 20 µg/day (Associate Committee on Scientific Criteria for Environmental Quality, 1973).

As regards the average daily intake in food, estimates from different countries and by different investigators vary from about 110 µg (Coulston et al., 1972 a, b & c; Boppel, 1975) to about 520 µg (Lehnert et al., 1969). These differences reflect different sampling techniques (duplicate portion or composite sample), different methods of analysis, but also different eating habits, sex and occupations. There is also a considerable difference between adults and children, the estimated intake for a breast-fed infant being about 40 µg (Alexander et al., 1973). Lead intake in food has apparently undergone no changes within the last 20 years; Horuguchi's (1974) comparison of daily intakes in 1950 and 1970 gave approximately the same value of about 200 µg for adults. Taking into account all the possible modifying factors, a recent WHO Task Group concluded that a fair estimate of daily intake of lead via food would be 200-300 µg (WHO, 1976).

Food is thus the major pathway of lead intake for the general adult population, contributing more than 80-85% of the total daily intake. Occupationally exposed persons and children have to be considered separately because the relative contributions of the various exposure pathways may be quite different.

6. Metabolism

6.1.1 Absorption of inhaled lead

Lead containing particles in the ambient air have an aerodynamic diameter of the order of 0.1-1.0 µm, and the predicted deposition in the airways would be about 35% (Task Group on Lung Dynamics, 1966). This is questionable for smaller particles (<0.1 µm) which are mainly deposited by diffusion (Lawther et al., 1972). The actual measurements of deposition in human volunteers gave results that differed considerably depending on the physical and chemical properties of inhaled aerosol. A value of 5-16% was obtained by Muir and Davies (1967), whereas Kehoe (1961) reported a deposition of 36 to 46% for lead (III) oxide particles with an average diameter of 0.9-2.9 µm. A high deposition was also observed by Nozaki (1966) ranging from 42.5-63.2% for 10 respirations per minute (1350 ml tidal air) and from 21-35% for 30 respirations/min (450 ml tidal air); the lower deposition values apply to the mass median diameter of 0.05 µm, the higher to 1.0 µm.

Overall deposition values alone are not sufficient to assess the contribution of inhaled lead particles to the body burden. Regional deposition as well as lung clearance has to be taken into account. For example Hursch et al. (1969) found that less than 6% of ^{212}Pb absorbed on natural room aerosols was deposited in the tracheobronchial tree compared to the total deposition of 14-45%. Large particles (2.9 µm) are probably deposited mainly in the nasopharynx and subsequently swallowed (Kehoe, 1961). High lead concentrations in air may damage clearance and other lung defense mechanisms as indicated by studies in vitro and in animals (Beck et al., 1973; Bruch et al., 1973 and 1976).

The rate of absorption of deposited leads depends on various factors, and particularly on the physico-chemical form of lead in particles. There is however no evidence of lead accumulations in the lungs, so that any lead compound once deposited is eventually absorbed or transferred to the gastrointestinal tract (Associate Committee on Scientific Criteria for Environmental Quality, 1973).

6.1.2 Absorption of ingested lead

Studies on the absorption of ingested lead indicate that about 10% is absorbed from the gastrointestinal tract (Kehoe, 1961; Rabinowitz et al., 1974). For children, the fraction absorbed may be much higher as pointed out by a recent study of Alexander et al. (1973) who found an absorption up to 53% in eight children aged from 3 months to 8 years. These results require verification because of the large scatter of values and the short period of study (WHO, 1976).

Values between 5 and 10% absorption were also obtained in animal studies (Horiuchi, 1970; Schlipköter and Pott, 1973). Here again, high values (50% or more) were observed for young animals with tracer doses of lead (Kostial et al., 1971; Forbes and Reina, 1972).

Animal studies have also shown that certain dietary factors such as milk, fasting, low calcium and vitamin D, iron deficiency may promote lead absorption (Kello and Kostial, 1973; Six and Goyer, 1972; Quarterman et al., 1976).

6.1.3 Estimates of total daily absorption

It is obvious that the total daily absorption of lead differs very widely for different populations and individuals. It may be, nevertheless, useful to have a rough estimate of this figure. With 10% absorption, the food would contribute 20-30 μg/day. Assuming an ambient air concentration of 1 μg/m^3, 20 m^3 of air intake per day, 30% deposition and complete absorption in the respiratory tract, inhalation with no occupational exposure could contribute up to 6 μg/day, by no means a negligible quantity. Drinking water would not contribute more than about 2 μg, assuming 1 liter daily intake and 10% absorption. The total absorption would be about 28 to 38 μg/day. A Canadian estimate is 21 μg/day (Associate Committee on Scientific Criteria for Environmental Quality, 1973).

6.2 Transport and distribution

Absorbed lead is transported by blood and initially distributed in various organs and tissues. It is then gradually re-distributed to form an exchangeable compartment (blood and soft tissues) and a storage compartment, essentially bone. In human subjects with low level exposure about 90% of the total body burden is found in bone. Barry (1975) found that in the United Kingdom the lead concentration in bones of men and women over 16 years of age ranged from 9-74 mg/kg wet weight. The concentration in liver was about 1 mg/kg and, in the kidney: 0.8 mg/kg in the cortex and 0.5 mg/kg in the medulla. Studies in the United States and Japan revealed similar concentrations and distribution patterns (Gross et al., 1975; Horiuchi et al., 1959). A comparatively high concentration was found in the aorta with atheroma (2.5 mg/kg wet weight, Barry, 1975). The same author reported that the mean lead concentration in the brain cortex of 50 adult males did not exceed 0.1 mg/kg wet weight with a range of individual values from 0.02-0.8 mg/kg; in the basal ganglia the range was 0.04-0.2 mg/kg.

Lead in blood is mainly bound to erythrocytes where its concentration is about 16 times higher than in the plasma (Butt et al., 1964). The manner in which lead combines with erythrocytes is not clear, but probably it is associated with hemoglobin (Barltrop and Smith, 1972).

Lead has also an affinity for membranes of the cell and mitochondria (Goyer and Krall, 1968) but not for lysosomes (Barltrop et al., 1971).

Lead in bone builds up throughout life; this does not apply to soft tissues where it stabilizes early in adult life; in some tissues it may even decrease with age (Gross et al., 1975).

Placental transfer of lead has been demonstrated by many authors (TGMA, 1973). There is a fairly good correlation between lead concentrations in the blood of mothers and newborn children (Haas et al., 1973; Hower et al., 1975), and the distribution in fetal tissues is similar to the distribution in the adult organism (Barltrop, 1969).

The total body lead content of a 70 kg man is of the order of 100-400 mg and increases with age (Associate Committee on the Scientific Criteria for Environmental Quality, 1973).

6.3 Elimination

About 90% of ingested lead is eliminated unabsorbed through feces (Kehoe, 1961; Tepper and Levin, 1972). Absorbed lead is excreted primarily in urine (about 76%); other excretion routes are gastrointestinal secretions (about 16%) and hair, nails and sweat (<8%) (Rabinowitz et al., 1973; Teisinger and Srbova, 1959). The rate of biliary excretion in man is not known. The mechanism of urinary excretion appears to be essentially glomerular filtration (Vostal, 1966).

Lead is also excreted in human milk in concentrations up to 12 µg/l (Horiuchi, 1970; Murthy and Rhea, 1971).

There is a considerable species variation for lead excretion in animals. In baboon, the dominant route of excretion is urine (Eisenbud and Wrenn, 1970) but in rat and sheep, biliary and transmucosal excretion may be higher than urinary (Castellino et al., 1966; Blaxter and Cowie, 1946).

6.4 Biological half-times

Assuming a total body burden of 80 mg of lead at the age of fifty, an average daily intake of 300 µg throughout life and 10% absorption from the gastrointestinal tract and applying an exponential one compartment model, Tsuchiya and Sugita (1971) obtained an estimate of 5 years for the total body half-time of lead.

The biological half-time for lead in human bone was estimated at about 10 years by TGMA (1973). A higher value was obtained when the recent study of Rabinowitz et al. (1974) was used as the basis of calculations (Task Group on Metal Toxicity, 1976). This model assumes three compartments: blood lead and some rapidly exchanging soft tissues with a $T_{1/2}$ about 19 days; soft tissues and a rapidly exchangeable bone fraction with $T_{1/2}$ about 21 days; and the skeleton with $T_{1/2}$ about 20 years. For all practical purposes the two first compartments can be combined.

7. Concentrations in tissues and body fluids as indicators of exposure and dose

7.1 Concentrations in biological media as indices of exposure

7.1.1 Lead in blood

Blood lead levels in human subjects with no known high exposure are fairly constant throughout the world, ranging from between 10 and 35 µg/100 ml on the average (Lehnert et al., 1970; NAS, 1972; Secchi and Alessio, 1974; Boudène et al., 1975; Tsuchiya et al., 1975). There do not seem to be any differences by age (US Department of Health, Education, and Welfare, 1975). Tsuchiya et al. (1976) showed clear differences in blood levels between men and women. This is consistent with other recent measurements of blood lead in women in Sweden (8.5 µg/100 ml, Haeger-Aronsen, 1961) and Finland (7.9 rural, 9.7 µg/100 ml urban, Nordman, 1975). There is a consistent difference between urban and rural populations, the latter showing lower values (US Department of Health, Education, and Welfare, 1965; Tepper and Levin, 1972). See Table 2.

Higher values are found in populations living near highways with heavy traffic (Waldron, 1975) and in the vicinity of lead smelters (Nordman et al., 1973; Martin et al., 1975). European studies indicate lower lead in blood (Pb-B) values in children than in adults (Haas et al.,1973; Grimes et al., 1975). This has been recently confirmed by Tsuchiya et al. (1976) who found Pb-B values in Tokyo children to be on the average about 8-10 μg/100 ml (Table 3).

In the USA, in some big cities, a large number of children were found with Pb-B concentration in the range of 40-80 μg/100 ml (Blanksma et al., 1969; Fine et al., 1972; Pueschel et al., 1972).

Lead levels in blood are under certain conditions a good indicator of exposure, and it is of interest to establish, if possible, the relationship between Pb-B and intakes by inhalation or ingestion.

A study by Sakurai et al. (1974) revealed the average concentration of lead in blood to be about 50 μg/100 ml in workers who had been exposed to a lead level of about 60 $\mu g/m^3$, 40 hours per week. However, the average lead concentration in air of 60 $\mu g/m^3$ was not a time-weighted average, but an average of 34 samples obtained from different sites within one large workroom at random times.

With regard to the relationship between lead levels in ambient air and blood lead concentration in the general population, the well-known Three Cities Study (U.S. Department of Health, Education, and Welfare, 1965) showed higher blood lead levels in those persons, e.g. policemen and drivers, who spend a good deal of their working hours outdoors. In another study about 150-200 housewives from 7 large U.S. cities and Los Alamos were examined for blood lead levels in the period from 1968-1971 (Tepper and Levin, 1975). The annual mean concentrations of lead in air were 0.14 $\mu g/m^3$ in Los Alamos to 4.55 $\mu g/m^3$ in Los Angeles. The geometric means of blood lead levels varied from 12.5 μg/100 ml to 20.15 μg/100 ml. There was no association between the atmospheric concentrations of lead in air and blood lea levels. However, when Hasselblad and Nelson (1975) analyzed the same data using a different statistical procedure, they concluded that the air lead gradient and the urban-suburban contrast contributed to the blood lead levels significantly with each explaining approximately 10 percent of the total area variation of blood lend concentrations. These two (not independent) comparisons explained more than twice as much of the total variation in blood lead as did either smoking or age.

Tsuchiya et al. (1975) studied the association between lead concentrations in the ambient air of Tokyo and blood lead levels of approximately 2,300 policemen. The greater Tokyo area was divided into 10 districts and one remote island 300 kilometers south of Tokyo was also included in the study. The annual average air concentrations of lead ranged from 0.024 μg/m³ on the island up to 1.3 μg/m³ in one Tokyo district. The concentrations in the other 9 districts varied from 0.2 μg/m³ to 1.0 μg/m³. The arithmetic means of blood lead levels ranged from 15.9 μg/100 ml to 20.6 μg/100 ml, showing a significant association between atmospheric lead concentrations and blood lead levels. However, blood lead levels on the island, where lead concentrations were the lowest, amounted to 17 μg/100 ml, a value higher than those found in two suburbs of Tokyo. The authors concluded that, in general, blood lead levels increase with urbanization, but that it was difficult to establish any direct relationship between lead levels in air and lead levels in blood and urine.

Griffin et al. (1975) exposed adult male volunteers 23 hours per day for about 18 weeks to airborne lead at 10.9 and 3.2 μg/m³. The particles of alpha lead dioxide were primarily of submicron size. The mean blood level of the men exposed to 10.9 μg/m³ reached a plateau of 37 μg/100 ml, after about three months of exposure. The blood lead level of the men exposed to 3.2 μg/m³ increased to about 27 μg/100 ml, and also leveled off after about three months.

The contribution of lead in air to Pb-B as inferred by Goldsmith and Hexter (1967) is about 1.3 μg of lead per 100 ml of blood for each increase of lead in air of 1 μg/m^3. Azar et al. (1973) estimated that about 1 μg/100 ml Pb-B corresponded to about 1 μg/m^3 lead in air (within the range of lead concentration of 2-9 μg/m^3). The data provided by Coulston et al. (1972 a, b & c) and by Rabinowitz et al. (1974) give values of about 3 and 1.2 μg/100 ml per 1 μg/m^3, respectively. These estimates apply to air concentrations below about 10 μg/m^3.

There is some supporting evidence for these estimates in animal studies. Griffin et al. (1975) exposed rats and Rhesus monkeys to airborne lead particles (0.05-0.10 μm) 22 hours per day at a mean concentration of 21.5 μg/m^3. A year-long exposure gave rise to an increase of the blood level to 28 μg/100 ml in rats and 17 μg/100 ml in monkeys. Levels of lead in the control animals were about 5 μg/100 ml in rats and 4 μg/100 ml in monkeys. Lead concentrations in the organs also showed elevated levels.

From these and other available studies, it is difficult to conclude whether there exists a consistent relationship between lead concentrations in ambient air and blood lead levels in the general population.

Estimates made on the basis of several studies on the relationships of Pb-B to the dietary lead intake (Coulston et al. 1972a, b & c; Zurlo and Griffini, 1973; Nordman, 1975) gave a range from 5.4-18.3 for men and 4.4-13 μg/100 ml per 100 μg oral lead intake per day for women (WHO, 1976).

7.1.2 Lead in urine

Lead concentrations in urine have been used for the medical surveillance of workers. Because of fluctuation of specific gravity of urine, spot samples are not a reliable indicator of exposure level.

Determinations of lead in urine may be useful for monitoring lead exposures of groups of workers, along with other indicator of excessive lead absorption. The lead content of normal urine varies from nondetectable levels up to 80 µg/l, with an average of about 30 µg/l (Elkins, 1959). However, recent studies on lead levels in urine in persons with no known high exposures to lead revealed much lower levels. Tsuchiya et al. (1975) indicated about 12 µg/l as a mean value obtained from 2,300 policemen in Japan.

Moderate lead absorption will give rise to an increase of 100-150 µg/l within a few weeks (Elkins, 1959). Values ranging from 150 to 200 µg/l may be considered as a borderline, and an excess of 200 µg/l is indicative of harmful exposure. According to the Subcommittee for Occupational Health of the Permanent Commission and the International Association of Occupational Health (Subcommittee Reports, 1969), 150 $\mu g/m^3$ lead in air corresponds to 130 µg/l lead in urine. Tsuchiya and Harashima (1965) concluded that for a 48-60 hour work week an average air lead concentration of 100 $\mu g/m^3$ would lead to an average urinary lead level of 150 µg/l.

It should be, however, noted that "normal" rates of lead excretion in urine may be found even when the exposure is high (WHO, 1976). Lead in urine following mobilization by chelating agents is discussed in Section 9.

7.1.3 Lead in teeth and hair

Lead concentrations in teeth and hair have been used as indicators of long-term exposure, but the information is inadequate for assessing their usefulness and reliability (WHO, 1976).

7.2 Concentrations in biological media as indices of concentration in critical organs

There is no information that could be used for assessing the concentration of lead in organs considered as critical (bone marrow, nervous system, kidney) from the concentrations of lead in blood, urine or other indicator media (Task Group on Metal Toxicity, 1976 ; WHO, 1976).

8. Effects and dose-response relationships

The following description of the effects and dose-response relationships is based mainly on human data. Animal data are used only as supporting evidence, when it is considered necessary.

Although the biological effects of lead in man are fairly well defined, the precise exposures or doses that are associated with the effects are rarely known.

There are few reports on the relationship between environmental concentrations and effects of lead. An example is Horiuchi and Ida's study (1955). In order to derive a maximum allowable concentration of lead in the air of the working environment they measured lead concentrations in the air of lead smelting plants, and estimated net exposures for workers in each plant by conducting a "time study" on each worker. They concluded that at 50 $\mu g/m^3$ lead in the air the values of the erythrocyte count and coproporphyrin excretion would remain normal, and that no signs of increased lead absorption would appear.

Some effects of lead are closely related to the measured levels of lead in blood, others are not. Lead in blood cannot be used as a reliable indicator of the exposure or dose for individuals, but it is most useful as an epidemiological indicator for assessing population exposure (WHO, 1976). The relationship between blood lead levels and the onset of a number of effects is shown in Fig. 1. Types of effects of inorganic lead salts as related to estimates of absorption are summarised in Table 4.

8.1 Local effects

There is no evidence that inhaled lead has local effects on the respiratory system in man, but the inhalation of lead (10 $\mu g/m^3$ for 3-12 months) by rats reduced the number of macrophages that could be flushed from lungs (Bingham, 1970). Damage of alveolar macrophages by lead was demonstrated in vitro (Beck et al., 1973).

Aub (1931) considered lead colic as a direct effect of lead on smooth muscle of the intestine, but this view is not generally accepted (Hamilton and Hardy, 1974).

8.2 Systemic effects

Lead may cause both acute and chronic effects which usually result from the accumulation of lead in the body over a certain period of time. The major effects are related to four organ systems, i.e. hemopoietic, nervous, gastrointestinal and renal. Symptoms, signs and pathology of inorganic lead poisoning have been described in a number of monographs (Cantarow and Trumper, 1944; Johnstone and Miller, 1960; Hunter, 1969; Waldron and Stöfen, 1974; WHO, 1976).

8.2.1 Acute effects

The most common form of acute lead poisoning is gastrointestinal. Acute lead poisoning may result both from short-term massive exposure and from long-term lead intake. After an initial stage of anorexia, symptoms of dyspepsia, and constipation, there is an attack of colic characterized by diffuse paroxysmal abdominal pain. The skin is usually pale, the pulse slow and the blood pressure may be increased. These signs and symptoms reflect the spasmodic contraction of smooth muscle, probably related to vagal irritation (Hamilton and Hardy, 1974).

Acute lead encephalopathy in adults is rare, but numerous cases have been observed in children with pica in the United States (NAS, 1972; Lin-Fu, 1976) and less frequently in Europe and Japan. Severe forms of encephalopathy develop suddenly with the onset of seizures and may result in coma and/or cardiorespiratory arrest. Prodromal manifestations rarely occur, but some children may have anemia and mild colic prior to the onset of the acute encephalopathy syndrome which includes vomiting, apathy, drowsiness, stupor, ataxia, hyperactivity and other neurological signs and symptoms. Lead concentrations in blood associated with acute encephalopathy may range from about 80-100 to 300 µg/100 ml (NAS, 1972; Chisolm, 1971).

8.2.2 Chronic effects

8.2.2.1 Hemopoietic system

Anemia is a common sign among occupationally exposed workers, although it is often so mild or moderate that it may not be detected unless observation on a group basis is carried out. Anemia due to lead is micro- or normocytic, but not macrocytic, being caused by a combined effect of the inhibition of hemoglobin synthesis and shortened life span of circulating erythrocytes.

The characteristic "pallor" associated with lead anemia is described less frequently in recent reports. This is probably due to the fact that past occupational exposures to lead were higher than they are today.

Increased numbers of basophilic stippled red cells and reticulocytes may also be seen in certain cases of lead anemia, but this is not pathognomic of plumbism. Nor are they good indicators for the study of dose-effect or dose-response relationships.

According to numerous studies performed in recent years, many stages in the pathway of heme synthesis are inhibited by lead, as summarised in Figure 2.

Delta-aminolevulinic acid dehydrase (ALA-D), which catalyses the formation of porphobilinogen from δ-aminolevulinic acid (ALA), and heme synthetase (heme-S), which incorporates iron into protoporphyrin IX (PP IX), are the enzymes most easily affected by lead (Eriksen, 1952; Dresel and Falk, 1956a, 1956b; avian erythrocytes were used in these studies in vitro). Higher lead concentrations also block the formation of ALA from glycine and succinate due to the inhibition of ALA-synthetase (ALA-S); coproporphyrinogen decarboxylase (CPG decarboxylase), which converts coproporphyrinogen (CPG) into PP IX, is also inhibited (Goldberg et al., 1956; Wada et al., 1972).

Wada et al. (1972) demonstrated a remarkable reduction in the activities of ALA-D and heme-S, a slight elevation of ALA-S activity, and a parallel reduction of ^{14}C-glycine incorporation into heme and globin in erythroid cells of bone marrow of lead-exposed workers. Increased activity of ALA-S contrasts with the in vitro observation of Goldberg et al. (1956).

Depression of ALA-D activity in erythrocytes following lead absorption has been observed in many studies (Lichtman and Feldman, 1963; Bonsignore et al., 1965; Hernberg and Nikkanen, 1972; Griffin et al., 1975). Partial inhibition of ALA-D is a useful indicator of lead absorption, but it is not regarded as a deleterious effect per se (Zielhuis, 1974) because the enzyme appears to possess a large reserve capacity. In more advanced states of lead absorption, there may be an increased excretion of δ-aminolevulinic acid in urine (ALA-U), and of coproporphyrin in urine (CP-U), an elevation of ALA in serum and an increase in free erythrocyte protoporphyrin (FEP) due to an effect of lead on the various stages of heme synthesis. These inhibiting effects will finally result in a reduction of heme synthesis and cause anemia.

The inhibition of ALA-D activity is correlated with the concentrations of lead in blood. Hernberg et al. (1970) showed a negative linear regression over a range of 5 to 90 μg/100 g Pb-B, when ALA-D was plotted on the logarithmic scale (Figure 3). ALA-D activity is inhibited by about 80% at a blood lead level of 50 μg/100 ml, and almost totally at the levels of 70-90 μg/100 ml. Similar results were reported by Millar et al. (1970) and Weissberg et al. (1971). However, a study by Sakurai et al. (1974) did not show statistically significant negative correlation in the control group, whereas Hernberg et al. (1970) found a correlation coefficient of -0.90 in a control group of 16 medical students. According to Sakurai et al. (1974), there is a limit of Pb-B about 20-30 μg/100 ml below which there is no decrease in ALA-D activity.

Similarly Wada et al. (1976) reported a limiting Pb-B level of about 15 μg/100 ml, below which ALA-D showed no correlation with Pb-B levels. Low precision in the determination of ALA-D levels may be a reason for the results obtained by Sakurai et al. and Wada. However, as shown in Figure 3, ALA-D activity of the erythrocytes of workers exposed to very low lead levels is nevertheless somewhat depressed in comparison with the control group, although Pb-B levels of both groups were found to be in the same range of 10-25 µg/100 g. The depression of ALA-D activity among lead workers with normal blood lead levels may imply that the workers have had higher blood lead levels some weeks prior to the date of blood sampling. There is a possibility that a qualitative change in the ALA-D molecule may persist after the blood lead level returns to normal.

Increased ALA excretion in urine has been observed at blood lead levels of 40-50 µg/100 g in many studies (Selander and Cramér, 1970; Hernberg et al., 1970; Haeger-Aronsen, 1971; Tsuchiya et al., 1972). However, the relationship between ALA in urine and blood lead levels is not linear. The increase of ALA in urine becomes very marked when the blood lead level exceeds 40-60 µg/100 g, as shown in Figure 4.

ALA in urine may also be related to age. Tsuchiya et al. (1975) found a negative correlation, higher ALA values being found in urine in younger age groups.

Coproporphyrin excretion in urine starts increasing at approximately 35-40 µg Pb/100 ml blood. According to Tola et al. (1973), it is almost as sensitive an indicator of lead absorption as ALA in urine.

PP IX in erythrocytes (free erythrocyte porphyrin, or FEP) is another sensitive indicator of lead absorption. Zielhuis (1975) concluded that there is a no-effect level of Pb-B for the increase of FEP at about 20-25 µg/100 ml in adult females and children, and at 25-30 µg/100 ml in adult males. This difference in blood lead levels among men, women, and children may possibly be explained by the difference in the sensitivity of FEP to iron deficiency or hemopoietic function.

An increase of the number of reticulocytes as well as basophilic stippled red cells is noted at blood lead levels of 60-80 µg/100 ml. However, in general, the degree of anemia does not correlate with blood lead levels. When blood lead level is about 70-80 µg/100 ml or more, frank anemia may develop in some individuals (Task Group on Metal Toxicity, 1976). However, good nutritional status may prevent recognizable lead anemia.

Another possible mechanism involved in the development of anemia is the shortening of the life span of erythrocytes. The exact manner in which the shortening of the life span occurs has not been elucidated, but it is most likely that the mechanical fragility and osmotic resistance of erythrocytes play an important role. A detailed discussion of this mechanism has been presented by Waldron and Stöfen (1974) and Task Group on Metal Toxicity (1976).

6.2.2.2 Nervous system

Increased lead absorption may give rise to effects on both the central and peripheral nervous systems. Effects on the central nervous system which are manifested as encephalopathy are seen more frequently in childhood lead poisoning from pica or other causes, possibly because children are more sensitive to the action of lead than adults (Lin-Fu, 1976). Subclinical effects on the peripheral nervous system have been reported in occupationally exposed workers.

It is sometimes difficult to make clear-cut distinctions between acute and chronic encephalopathy because the so-called chronic encephalopathy may be either an effect on the brain of a long-term exposure to lead or a residual effect of an acute episode of encephalopathy. The severity of encephalopathy depends on a combination of factors which include intensity and duration of exposure, and age.

Milder symptoms of the effects on the central nervous system may include mental deterioration, hyperkinetic or aggressive behavior, loss of appetite, difficulty in sleeping, abdominal pain, and vomiting. However, the etiology of such manifestations is not always clear, because those children who suffer from cerebral injury due to traumatic, toxic, viral or bacterial agents often incur persistent pica which may in turn result in elevated intake of lead (NAS, 1972). Neurological sequelae of acute lead encephalopathy have been reported by Chisolm (1973); in severe cases they may include convulsions, cortical atrophy, hydrocephalus, and idiocy; in milder cases there is lack of motor coordination and sensory perception (WHO, 1976).

Subclinical neurophysiological effects may be observed among young children with moderately elevated blood lead levels, between 40 and 80 µg/100 ml (Lin-Fu, 1976). David et al. (1972) observed higher lead levels and higher post penicillamine urine lead levels among the children with hyperactivity than in the control children. However, from this study, it could not be concluded whether lead exposure was caused by hyperactivity or whether hyperactivity was caused by lead exposure. Landrigan et al. (1975) observed neurological dysfunction in 46 symptom-free children 3-15 years of age with moderately elevated blood lead concentrations (mean: 48 µg/100 ml) and compared them to children who showed less than 40 µg/100 ml (mean: 27 µg/100 ml). The first group showed lower scores (Wechsler Intelligence Scale) and poorer results in the fingerwrist tapping test than the second group, but there were no differences between the groups in full-scale I.Q., verbal I.Q., behavior or hyperactivity ratings. This study, however, did not present conclusive evidence of lead as the causative factor. Lin-Fu (1976) cites some animal studies which suggest that hyperactivity might result from moderate lead exposure via mother's milk.

It is not certain whether a Pb-B level in children below 100 µg/100 ml can be associated with an increase in prevalence of mental retardation (Perlstein and Attala, 1966) or hyperactivity (David et al., 1972). Recently, Zielhuis (1975) concluded that there is some evidence that no-effect Pb-B levels for chronic encephalopathy are somewhat lower in children (probably at 50-60 µg/100 ml) than in adults (about 80 µg/100 ml). Since chronic effects on the central nervous system may be a consequence of repeated high exposures, it is difficult to evaluate dose-effect and dose-response relationships unless careful follow-up studies, including exact information on previous lead exposures, are performed.

Reports on peripheral lead neuropathy have been rare in recent years. In the past, wrist drop caused by palsy of the N. radialis was observed among lead workers with severe exposure. In rare cases foot drop accompanied wrist drop.

Peripheral neuropathy is characterized by the involvement of motor neurons but with little sensory involvement. Subclinical neuropathy may be detected by electrophysiological techniques (Seppäläinen and Hernberg, 1972). Nerve-conduction velocity measurements can be used for early detection of overexposure, but not for diagnosis of lead poisoning in individuals (Seppäläinen et al., 1975).

A statistically significant ($P<0.02$) reduction of the peripheral nerve conduction was observed in a group of 24 children with known lead absorption (Pb-B 40 µg/100 ml; more than 600 mg Pb excreted in urine per 24 h) (Feldman et al., 1973).

Slowdown of nerve conduction in the upper extremities, particularly in the slower fibers and distal portion, and electromyographic abnormalities such as fibrillations and diminished number of motor units on maximal contraction, were found in lead workers with a mean lead blood level of 40 ± 9 µg/100 ml (maximum 65 µg/100 ml) and no signs of lead poisoning (Seppäläinen et al., 1975).

There was no correlation between neurological tests and the biochemical indices of exposure. According to Hernberg (1976) the no-observed-effect Pb-B level for such effects is most likely about 50 µg/100 ml (Fig. 1) but a more precise evaluation of the degree of exposure is needed to confirm these findings.

8.2.2.3 Gastrointestinal tract

Lead colic may occur at comparatively low levels of exposure in industrial workers (40-80 µg/100 ml Pb-B, Beritic, 1971) and in children and infants. It is usually accompanied by other signs of poisoning. There is not enough data to establish a dose-effect or dose-response relationship (WHO, 1976).

8.2.2.4 Kidney

Few reports are available on occupational lead poisoning associated with nephropathy (Clarkson and Kench, 1956; Goyer et al., 1974). On the other hand, renal tubular dysfunction has been reported in children (Marsden and Wilson, 1955; Chisolm and Leahy, 1962). People who consume lead-contaminated whiskey may also show impairment of the renal tubular transport mechanism (NAS, 1972).

Renal functional disturbances in children, similar to those seen in the Fanconi syndrome, are characterized by aminoaciduria, glucosuria, and hyperphosphaturia with hypophosphatemia (Ferm and Carpenter, 1967).

Degenerative changes in the proximal tubular lining cells involve mitochondrial swelling. Eosinophilic dense staining nuclear inclusion bodies, which indicate a more specific change, have also been observed. The inclusion bodies seen in lead poisoning have a characteristic outer fibrillar margin, recognizable by electron microscopy, which is useful in distinguishing them from other nonspecific bodies (Task Group on Metal Toxicity, 1976)

They are excreted during EDTA administration and may contain lead which is mobilized by EDTA (Goyer et al., 1974). All these functional and morphological changes are reversible upon treatment with chelating agents such as EDTA, but only in cases of relatively short-term lead exposure (Chisolm and Leahy, 1972). Lead in blood levels associated with such effects may range from 40-120 µg/100 ml (Pueschel et al., 1972).

Long-term exposure to lead may give rise to the development of irreversible functional and morphological renal changes. These consist of intense interstitial fibrosis, tubular atrophy and dilatation. The involvement of glomeruli may occur at a relatively later stage. A consequence of such chronic renal damage may be saturnine gout in which uric acid level is increased in urine (Emmerson, 1968). However, it is not well known whether the pain in the joints often seen in cases of lead poisoning is directly related to the increase of uric acid in urine.

It is still controversial whether an exposure to lead in childhood is likely to be associated with occurrence of nephropathy in later life. There is one study from Australia which shows that a long-term exposure to lead early in life may later result in chronic nephropathy which is identical to the chronic nephropathy observed in adult cases of lead poisoning (Emmerson, 1968). On the other hand Tepper (1963) and Chisolm (1970) in the Unites States performed 10-20 year follow-up studies on children who had suffered lead poisoning and found no increase of nephropathy later in life.

A WHO task group concluded that prolonged exposure to lead associated with Pb-B levels above 70 μg /100 ml may result in chronic irreversible nephropathy (WHO, 1976).

8.2.2.5 Liver

There have been relatively few recent reports on the liver in relation to lead poisoning. Quoting a 1934 study of Flury, Cantarow and Trumper (1944) mentioned that the disturbances in liver function probably precede the actual morphological changes in the liver cells. Tsuchiya et al. (1955) performed serum fraction analyses on lead workers in Japan. They noted an increase of A/G ratio in serum on a group basis, which may be related to subclinical effects on the liver. A study by Cooper et al. (1973) revealed a statistically significant correlation between blood lead levels and SGOT values, but it is doubtful that lead may cause significant functional and morphological changes in the liver. More detailed examinations in highly exposed subjects may show some minor functional changes.

8.2.2.6 Cardiovascular system

According to Dingwall-Fordyce and Lane (1963) workers who had been exposed to high levels of lead in the years before retirement showed higher risk of cerebrovascular accidents than other retired workers who had been exposed to lower lead levels or not exposed at all. A study by Cooper and Gaffey (1975) in the United States did not confirm Dingwall-Fordyce and Lane's results. This may be due to a difference in lead exposure, i.e. workers were formerly exposed to much higher levels of lead than is the case now. There may also be other factors involved, since the workers in the Dingwall-Fordyce and Lane study who had been exposed to high levels of lead were selected from a different socioeconomic stratum than other workers in the same study who had been exposed to lower levels.

The association between hypertension and lead exposure has not been clarified (Cramer and Dahlberg, 1966; Monaenkova and Glotova, 1969). There are several reports suggesting that electrocardiographic abnormalities in man could be caused by lead (Myerson and Eisenhauer, 1963; Freeman, 1965; Silver and Rodriguez-Torres, 1968).

8.2.2.7 Endocrine organs

The possible effects of lead on endocrine organs include impairment of thyroid and adrenal function, and disturbance of tryptophan metabolism (Sandstead et al., 1970; Urbanowicz et al., 1969), but the latter effect could not be confirmed by Schiele et al. (1974). The interpretation of these findings is difficult at present (Task Group on Metal Toxicity, 1976).

8.3 Carcinogenic, teratogenic and genetic effects

8.3.1 Carcinogenic effects

Although there is no evidence that lead is carcinogenic to man, there are several reports in which benign and malignant tumors were produced in experimental animals. In most of the available studies malignant and benign renal neoplasms were induced in mice and rats by oral or parenteral administrations of various types of lead compounds in rather high doses. A report published by the International Agency for Research on Cancer (IARC, 1972) concluded that there was no evidence to suggest that exposure to lead salts causes cancer in any sites in man. The level of human exposure equivalent to the levels of lead acetate producing renal tumors in rats would be 810 mg/day (550 mg Pb).

8.3.2 Teratogenic effects and effects on reproduction

Stillbirths and miscarriages have often been reported as a possible result of exposure to lead (Cantarow and Trumper, 1944), but there is no epidemiological evidence to support these claims. Similarly, there is no evidence that lead affects in any way the *in utero* development of the fetus in man, although there are some experimental studies in animals that indicate that lead may have some effects on litter size, weight, survival rate and possibly behavior (Stowe and Goyer, 1971; Snowdon, 1973).

8.3.3 Genetic effects

The evidence on a possible association of lead exposure and chromosomal aberrations in man is inconclusive and contradictory. This may be due to the fact that in several studies exposure was mixed (Pb, Zn, Cd) (Deknudt et al., 1973; Schwanitz et al., 1975; Bauchinger et al., 1976). The available experimental data are too scarce to clarify this question (Muro and Goyer, 1969).

8.4 Modifying factors and interactions

There is some indication that certain biological effects of lead occur at lower Pb-B levels in children than in adults (Roels et al., 1975; Zielhuis 1975; Lin-Fu, 1976). It has been noted that severe lead poisoning in children occurs more frequently in summer, but the reasons are not clear (Baetjer, 1959). The evidence favoring an influence of dietary composition on the susceptibility to lead is almost entirely experimental. Low phosphorus, calcium and iron enhance lead absorption and low protein diet appears to increase the susceptibility to lead poisoning (Six and Goyer, 1970; Goyer and Mahaffey, 1972; Mahaffey, 1974). Interactions of lead with other metals are poorly understood. There seems to be a synergistic interaction between lead and cadmium in experimental teratogenesis (Ferm, 1969), whereas zinc appears to be antagonistic to lead (Willoughby et al., 1972; Cheh and Neilands, 1973).

9. Diagnosis, treatment and prognosis of lead poisoning

9.1 Diagnosis

The value of diagnostic tests in lead poisoning has been recently reviewed by a WHO group of experts (WHO, 1976). For differential diagnosis of lead poisoning it is essential to determine lead in blood and δ-aminolevulinic acid and coproporphyrin in urine. Other tests including ALA-D activity, hemoglobin, FEP and basophilic granulation may provide useful supplementary information.

Subjects who have developed symptoms some months prior to diagnosis and who have been removed from exposure at the time of development of symptoms may require calcium-EDTA provocation tests, since blood lead levels in these cases may have returned to almost normal at the time of diagnosis. If urinary lead excretion within 24 hours after one gram of calcium-EDTA intravenous infusion exceeds one milligram, such subjects are considered to have had abnormally high lead exposure in the past (Rieders, 1960). According to a technique reported by Emmerson (1963), the upper limit in healthy adult subjects is less than 600 µg lead excreted over 4 days after a one gram injection of calcium-EDTA.

Early detection of health impairment due to occupational lead exposure has been extensively discussed in a recent report of a WHO Study Group (WHO, 1975).

9.2 Treatment

The first and foremost measure to be taken in any case of lead poisoning is, of course, removal of the victim from the source of exposure. Chelating agents which may be used in treating cases of both acute and chronic lead poisoning are BAL (British Anti-Lewisite), calcium-EDTA (monocalcium ethylene diamine tetra-acetic acid) and D-penicillamine. Calcium-EDTA is the agent most widely and effectively used. Abdominal colic and wrist drop disappeared completely after a few courses of calcium-EDTA injections, leaving no sequel to the poisoning (Nakasawa et al., 1969). The present author believes that calcium-EDTA has fewer side effects than BAL. Dose schedules for treatment of lead poisoning by the three above-mentioned chelating agents are summarized in Table 5.

The daily dose should not exceed 220 mg/kg body weight every 12 hours since calcium-EDTA can cause hazardous effects (Aronsen et al., 1968). For children, intravenous doses should not exceed 75 mg/kg every 6 to 12 hours (Chisolm, 1973). Side effects such as lacrimation, nasal congestion, sneezing, muscular pains and hypotension may be seen during or after treatment by calcium-EDTA (Waldron and Stöfen, 1974). Chronic renal damage with reduced clearance is a contraindication for the use of calcium-EDTA or D-penicillamine. Chelating agents should not be administered orally or intravenously for preventive purposes. However, in pediatric emergency, if blood lead level exceeds 80 µg/100 ml, even though no symptoms are recognizable, immediate chelation therapy by calcium-EDTA is recommended (Chisolm, 1973). For more detailed information on treatment of lead poisoning, the reader is referred to the handbooks by Krupp and Chatton (revised annually) and Cecil-Loeb Textbook of Medicine (revised every 3 years).

9.3 Prognosis

Anemia, gastrointestinal disturbances and neurological disorders caused by lead poisoning are generally considered completely curable by proper treatment if diagnosis is made. A slight or moderate renal tubular disorder which occurs at an early stage of lead poisoning is considered reversible. In childhood lead poisoning, residual effects on the central nervous system are common (NAS, 1972).

In general, if workers who show moderate or subclinical signs of lead poisoning are removed from exposure, signs or subclinical symptoms will disappear within a few weeks to several months.

10. Tetraethyllead

One of the alkyl compounds, tetraethyllead (TEL), is widely used as an anti-knock agent in motor fuels. The amount used varies in different countries, but in general is about 0.1% of the fuel content. The combustion of TEL in motor fuel is the main source of lead in ambient air. Almost all the TEL is decomposed by combustion into inorganic lead compounds such as lead halides and oxides, but very small amounts of organic lead which have not been affected by combustion escape into the ambient air. According to a survey conducted by the U.S. Department of Health, Education and Welfare (1965), TEL concentrations in ambient air did not reach 10% of inorganic lead values and were probably considerably less than 10%. The concentrations of TEL in urban areas at present are too low to have adverse effects on the health of the general population.

Since TEL is very volatile, the absorption is usually by inhalation, but the liquid is easily absorbed by the skin as well as by the gastrointestinal tract. After absorption TEL is distributed to various tissues, particularly to the brain and other organs, decomposing into triethyl lead and minute amounts of inorganic lead in the tissues and organs, mainly in the liver, and is excreted rapidly into urine.

Bolanowska et al. (1967) studied the metabolism of TEL using three accidental cases of acute fatal poisoning. The highest concentrations of both triethyl and total lead were found in the liver of all three cases, and in descending order of content, in the kidneys, pancreas or brain, and heart. The person who had ingested the TEL showed the highest concentration of both triethyl and total lead. The couple who had inhaled TEL showed much lower concentrations of triethyllead in all the above-mentioned organs except the liver. This indicates that TEL is metabolized to triethyllead within a short time period, i.e. within hours of absorption. Triethyllead may be retained in the body more than 20 days, although the average concentrations of triethyllead in the tissues diminish very rapidly. High urinary lead levels (400-800 μg/l) were observed, indicating that triethyllead is excreted into urine within a relatively short period of time, partially metabolized into inorganic lead.

The acute toxicity of TEL is much higher and the poisoning is quite different from that caused by inorganic lead.

Accidental exposure to TEL may result in lack of appetite, nausea, vomiting, and diarrhea. Complaints of irritability, restlessness, nervousness, and anxiety may develop before severe symptoms appear. These acute or subacute symptoms have seldom been reported in recent years among workers who produce TEL, because of improvements in production methods, and also because of early detection of accidental exposure by the monitoring of lead levels in air and urine. However, accidents may occur in instances where TEL-containing gasoline storage tanks are cleaned or where cargos of TEL are transported by ship.

The earliest symptom of TEL poisoning is insomnia, and the main organ affected is the central nervous system. The poisoning is usually acute, developing into toxic psychosis with hallucinations, delusions, excitement, and bad dreams, and may result in death. If mental symptoms cease and death does not occur, the patient usually recovers without sequelae after 2 to 3 months. Abdominal pain and peripheral neuropathy, which are common symptoms of inorganic lead poisoning, have seldom been observed in cases of TEL poisoning.

Cassels and Dodds (1946) and Kehoe (1942) agreed that if the urinary excretion of lead is less than 100 μg/l at the time symptoms such as those mentioned above develop, the cause is probably not the absorption of TEL. If the urinary concentration is about 150 μg/l, mild symptoms may develop, but TEL poisoning is usually associated with concentrations of 300 μg/l or more. Chronic exposure to TEL in which lead in urine was 64 ± 33 μg/l did not give rise to adverse effects on health (Stopps et al., 1966).

Since organic lead is excreted into urine rather rapidly, there is little possibility of inorganic lead poisoning occurring due to exposure to TEL.

The most important measure for detecting accidental exposure and for preventing early effects of TEL is the periodic monitoring of urinary lead levels and of lead concentrations in the air of working environments.

Table 1. Air lead concentrations in some cities of the European community 1971-72 (From CEC, 1973).

Location	Continuous measurements	Traffic-hour measurements
Non-urban	monthly means < 0.5 $\mu g/m^3$ daily maxima < 1 $\mu g/m^3$	-
Small cities:		
residential areas	monthly means < 1 $\mu g/m^3$ daily maxima < 2 $\mu g/m^3$	-
traffic areas	-	monthly means < 3 $\mu g/m^3$ individual measurements < 8 $\mu g/m^3$
Metropolitan areas:		
residential areas	monthly means < 2 $\mu g/m^3$ daily averages up to 8 $\mu g/m^3$	individual measurements < 4 $\mu g/m^3$
traffic areas	monthly means up to 6.5 $\mu g/m^3$ daily maxima up to 10 $\mu g/m^3$	monthly means <10 $\mu g/m^3$ single measurements up to <20 $\mu g/m^3$

Table 2. Levels of blood lead, urinary lead, urinary coproporphyrin and δ-ALA in urine of Tokyo inhabitants (From Tsuchiya, 1976).

	PbB (μg/100 g)		PbB (μg/g)		Copro (μg/l)		ALA (μg/l)	
	mean	S.D.	mean	S.D.	mean	S.D.	mean	S.D.
Total	13.06**	7.56	12.39**	10.18				
male	14.98	7.98	13.12	10.26				
female	11.22	6.64	11.70	10.06				
Total for 1970	12.12**	6.31	12.06**	9.19	50.00**	39.67		
male	13.72	6.58	12.89	9.53	54.37	44.26		
female	10.38	5.59	11.15	8.65	44.94	32.94		
Total for 1971	14.06**	8.56	12.73*	11.10			1.84**	0.90
male	16.52	9.20	13.39	11.00			1.58	0.96
female	12.01	7.47	12.18	11.16			1.72	0.83

* Significant sex difference (P < 0.05)

** Significant sex difference (P < 0.01)

Table 3. Means and standard deviations of lead in blood and urine and ALA-D in urine (From Tsuchiya, 1976).

	Blood lead (µg/100 ml)	Lead in urine (µg/l)	ALA-D in urine (mg/l)
Urban			
Male children	9.8±2.9* (78)	5.5±3.1 (78)	3.3±1.1 (78)
Female children	8.1±2.4* (74)	4.9±2.9 (66)	3.1±1.0 (67)
Suburban			
Male children	7.9±2.4 (84)	4.8±2.3 (83)	3.2±1.0 (84)
Female children	5.4±1.8 (67)	4.5±1.8 (66)	3.1±0.9 (67)

* Significant difference ($P < 0.01$) between urban and suburban children. Number of persons examined is given in parentheses.

Table 4. Level and types of effects of inorganic lead salts as related to estimates of various levels of absorption - recent and remote (From NAS, 1972).

Type of effects	Level I: No demonstrable in vivo effect	Level II: Minimal subclinical metabolic effect	Level III: Compensatory biologic mechanisms invoked	Level IV: Acute lead poisoning		Level V: Late effects of chronic or recurrent acute lead poisoning
				Mild	Severe	
Metabolic (accumulation and excretion of heme precursors)	Changing ALA-D	Slight increase urinary ALA may be present	ALA, UCP, FEP progressively increased	ALA, UCP, FEP increased 5 to 100 fold		Increased if excessive exposure recent, but may not be increased if excessive exposure remote
Functional injury:						
Hematopoiesis	None	Not known	Shortened red-cell life-span, reticulocytosis (±) (reversible)	Shortened red-cell life-span and reticulocytosis with or without anemia (reversible)		Anemia (±) (reversible)
Kidney (renal tubular function)	None	Not known	?	Aminoaciduria, glycosuria (±) (reversible)	Fanconi syndrome (reversible)	Chronic nephropathy (permanent)
Central nervous system	None	Not known	?	Mild injury (??? reversible)	Severe injury (permanent)	Severe injury (permanent)

3

Type of effects	Level I: No demonstrable in vivo effect	Level II. Minimal subclinical metabolic effect	Level III: Compensatory biologic mechanisms invoked	Level IV: Acute lead poisoning		Level V: Late effects of chronic or recurrent acute lead poisoning
				Mild	Severe	
Peripheral nerves	None	Not known	?	Rare	Rare	Impaired conduction (wrist, foot drop usually improve slowly, but may be permanent)
Clinical effects	None	Not known	Nonspecific mild symptoms (may be due in part to coexisting diseases)	Colic, irritability, vomiting	Ataxia, stupor, coma, convulsions	Mental deficiency (may be profound), seizure disorder, renal insufficiency, (gout) (permanent)
Index of level of recent or current absorption:						
Blood lead, µg/100 g of whole blood	<40	40-69	50-100+	>80 With anemia, intercurrent disease: 50-100+	>80	May be normal
Urine lead (adults only), µg/l	-	<80	<130	>130 (May be less in severe illness)	>130	Spontaneous excretion may be normal

Table 5. Dosage schedules for treatment of lead poisoning (From Waldron and Stöfen, 1974).

Drug	Dose	Route	Contra-indications
BAL	18 mg/kg/24 hr for 2 days 12 mg/kg/24 hr for 1 day 6 mg/kg/24 hr for 7 days	Deep intramuscular	Hepatic disease
Ca-EDTA	50 mg/kg/24 hr for 5 days Allow 2 days before starting a second course	Intravenous or intramuscular	Kidney disease
D-penicillamine	0.9-1.5 g/24 hr	Oral	Kidney disease

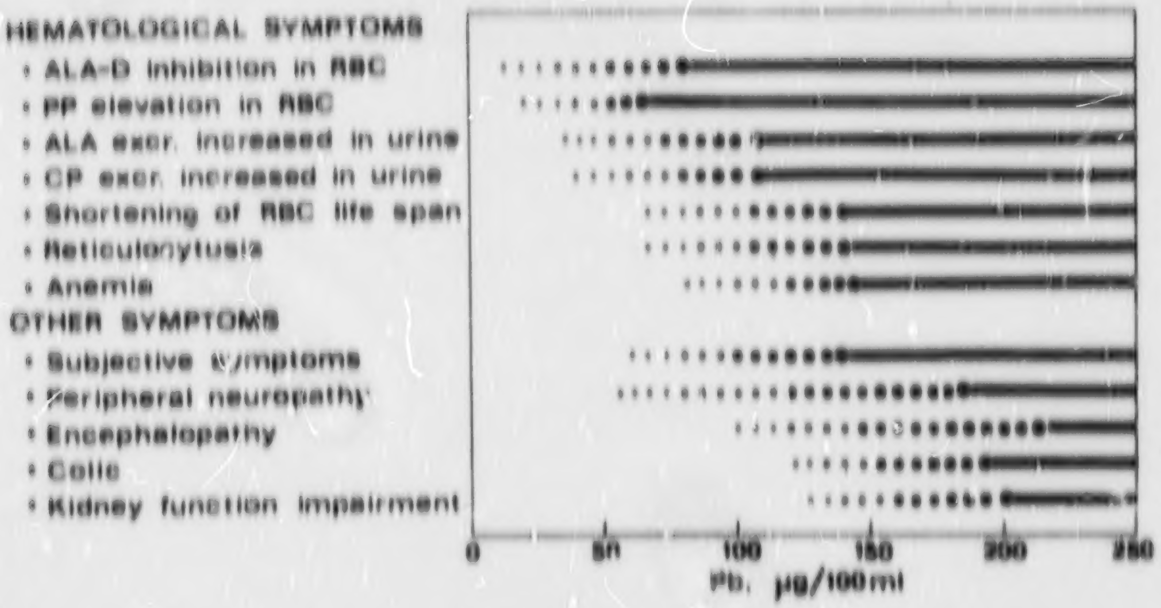

Figure 1. Relationship between blood lead levels and the onset of a number of effects (From Hernberg, 1976).

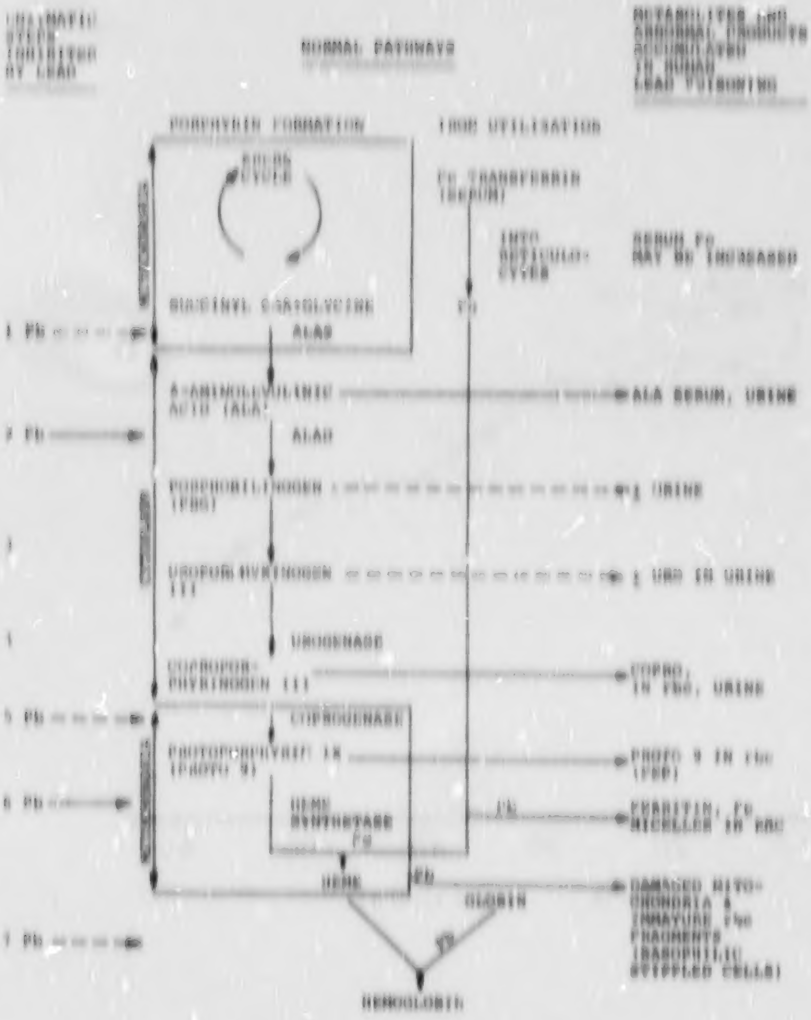
ENZYMATIC STEPS INHIBITED BY LEAD
NORMAL PATHWAYS
METABOLITES AND ABNORMAL PRODUCTS ACCUMULATED IN HUMAN LEAD POISONING
PORPHYRIN FORMATION
IRON UTILIZATION
KREBS CYCLE
Fe TRANSFERRIN (SERUM)
INTO RETICULOCYTES
SERUM Fe MAY BE INCREASED
SUCCINYL CoA+GLYCINE
Fe
1 Pb
ALAS
δ-AMINOLEVULINIC ACID (ALA)
ALA SERUM, URINE
2 Pb
ALAD
PORPHOBILINOGEN (PBG)
↑ URINE
3
UROPORPHYRINOGEN III
↑ URO IN URINE
4
UROGENASE
COPROPORPHYRINOGEN III
COPRO, IN RBC, URINE
5 Pb
COPROGENASE
PROTOPORPHYRIN IX (PROTO 9)
PROTO 9 IN RBC (FEP)
6 Pb
HEME SYNTHETASE
Fe
FERRITIN, Fe MICELLES IN RBC
HEME
Pb
GLOBIN
DAMAGED MITOCHONDRIA & IMMATURE RBC FRAGMENTS (BASOPHILIC STIPPLED CELLS)
7 Pb
Pb
HEMOGLOBIN

Figure 2. Lead interference with the biosynthesis of heme during several enzymatic steps, with the utilization of iron, and, in erythrocytes, with globin synthesis (From NAS, 1972).

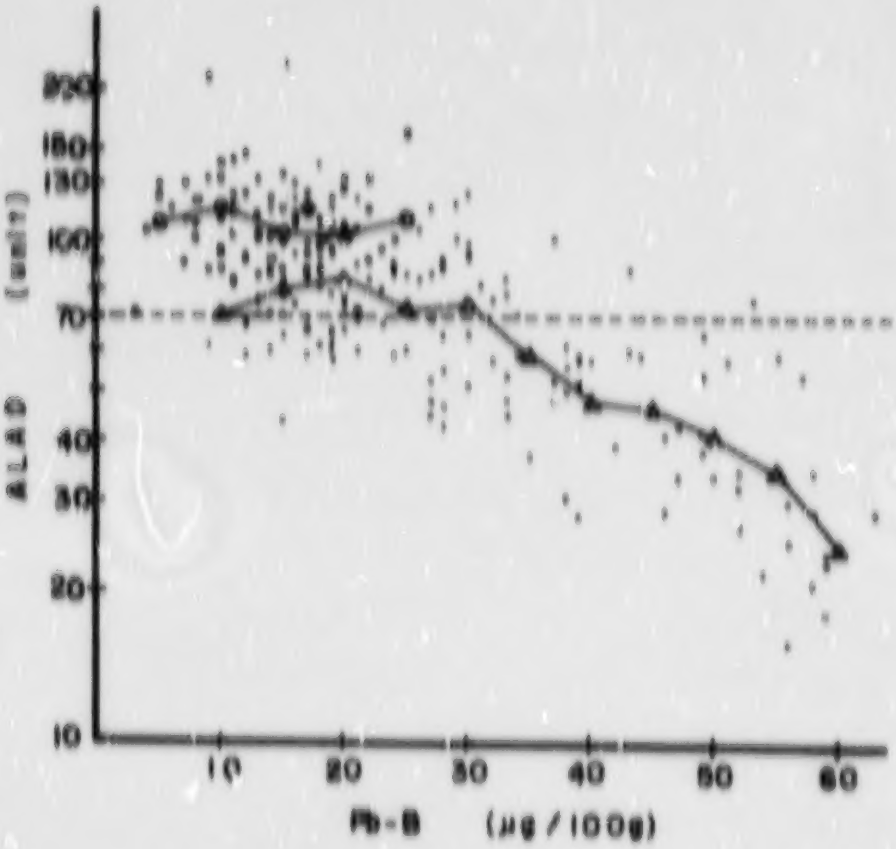

Figure 3. Relationship between blood lead concentration (Pb-B) and erythrocyte ALAD. Open circles, control group. Solid circles, Pb group. Broken lines indicate the means of ALAD for every 5 ug/100 g subcategories of Pb-B. Transverse dotted line is the lower 95% confidence limit (two-tailed) (From Sakurai et al., 1974).

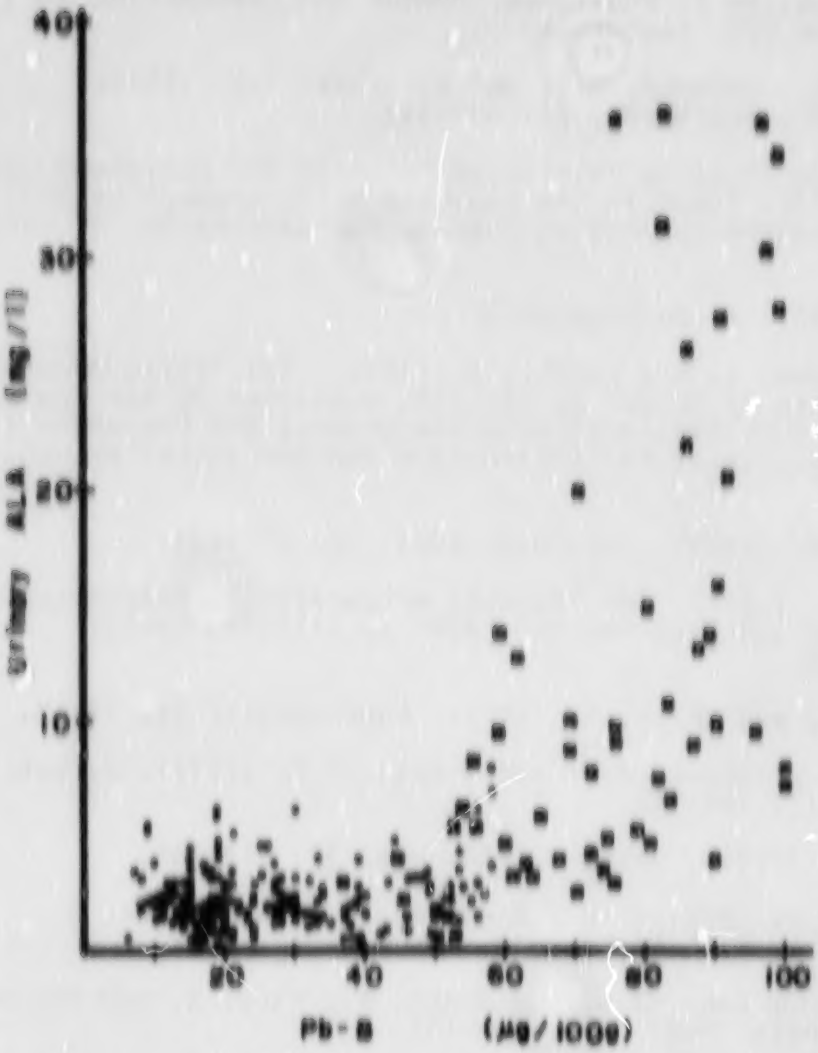

Figure 4. Relationship between blood lead concentration (Pb-B) and urinary ALA. Solid circles, data from rubber hose and automobile tire factory; open squares, data from storage battery factories (From Sakurai et al., 1974).

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MERCURY

Maths Berlin

1. Abstract

Mercury occurs as inorganic and organic compounds (mercury vapor, mercury liquid, mercury salts, short-chain alkylmercury compounds, alkoxyalkylmercury compounds and phenylmercury compounds), all having different toxicological properties.

Mercury can be analyzed in water, air and biological material by atomic absorption methods and by neutron activation analysis, and can be detected down to concentrations of a tenth of a ng. Methylmercury can be detected in biological material at levels of a few ng by extraction with benzene after strong acidification with hydrochloric acid, followed by gas chromatographic analysis of methylmercury chloride.

Mercury is circulated naturally in the biosphere, 30,000 - 150,000 tons being released to the atmosphere by degassing from the earth's crust and the oceans. In addition, 20,000 tons of mercury are released into the environment each year by human activities such as combustion of fossil fuels and other industrial release. 10,000 tons of mercury are produced yearly for industrial use, a small part of which is used for synthetizing organic mercury compounds.

In nature, mainly in the aquatic environment, methylmercury is produced from inorganic mercury by a microbial activity. In fish, the major amount of mercury is methylmercury.

The toxic properties of mercury vapor are due to mercury accumulation in the brain causing neurological signs involving an unspecific asthenic vegetative syndrome (micromercurialism). At higher exposure levels mercurial tremor is seen, accompanied by severe behavioral and personality changes, increased excitabi-

ity, loss of memory and insomnia. On a group basis, exposure levels are likely to be reflected in mercury concentration in blood and urine. Occupational exposure to mercury concentrations in air above 0.1 mg/m^3 may produce mercurialism. Micromercurialism has not been reported at concentrations below 0.01 mg/m^3.

The acute and long-term action of mercuric salts, phenylmercury compounds and alkoxyalkylmercury compounds is likely to be gastrointestinal disturbance and renal damage - appearing as a nephrotic syndrome with tubular necrosis in severe cases. The lethal dose in man is about 1 g of mercuric salt. The mercury load on the kidney is best determined by analysis of renal biopsy. Mercury concentrations of kidney between 10-70 mg/kg have been reported in poisoned cases. Levels below 3 mg/kg may be found in normal cases. Occasionally, mercuric compounds may cause idiosyncratic skin symptoms which may develop into severe exfoliative dermatitis. A specific form, called acrodynia or pink disease, is seen in children. Most cases show increased levels of mercury in urine.

The hazards involved in long-term intake of food containing methylmercury or occupational exposure to methylmercury are due to the efficient absorption (90%) of methylmercury in man and the long retention time - half-time 70 days - with accumulation of methylmercury in the brain. Chronic poisoning results in degeneration and atrophy of the sensory cerebral cortex, paresthesia, ataxia, hearing and visual impairment. Prenatal exposure causes cerebral palsy. Methylmercury concentration in blood and hair reflects the body burden and the concentration in brain of methylmercury. Intake resulting in body burdens exceeding 0.5 mg/kg body weight is likely to give neurological signs. This intake corresponds to blood values exceeding 200 μg/l and mercury levels in hair exceeding 50 mg/kg. Cerebral palsy may result from a lesser intake of methylmercury.

The history of mercury toxicology has been reviewed by Goldwater (1974), the pharmacology and toxicology by Clarkson (1972), the toxicology of methylmercury by a Swedish Expert Group (1971), toxicology and epidemiology by Friberg and Vostal (1972), Task Group on Metal Accumulation (1973), Task Group on Metal Toxicity (1976) and Task Group on Environmental Health Aspects of Mercury (1976).

2. Introduction

Mercury is a metal which is in liquid state at room temperature. In addition to its metallic state, mercury occurs in compounds as monovalent mercurous mercury and divalent mercuric mercury. Mercury also exists in nature as organometallic compounds in which mercury is covalently bound to carbon, in compounds of the type RHg^+ and $RHgR'$ where R and R' represent the organic moiety. The carbon-mercury bond is chemically stable due to the low affinity of mercury for oxygen.

The affinity of mercury for sulfur and sulfhydryl groups is a major factor behind the biochemical properties of mercury and mercury compounds. The mercury-containing moiety binds to sulfhydryl groups of proteins in membranes and enzymes, thereby interfering with membrane structure and function and with enzyme activity. Thus mercury compounds which can form mercury-containing radicals or ions of type RHg-, RHg^+ or Hg^{++} are generally cytotoxic as sulfhydryl groups are ubiquitous in organisms. The molecular structure of the mercury compound, its stability in the organism and its routes of biotransformation and excretion will govern the toxicological properties for the higher organisms. Thus each mercury compound has its own toxicology in relation to dose-effect and dose-response relationships.

From the toxicological point of view, it is convenient to divide the mercury compounds into inorganic compounds and organic compounds. Among the inorganic compounds, elemental mercury and the divalent mercury salt are the compounds of toxicological interest. It is doubtful whether mercurous mercury has any survival in the organism, although at present the possibility cannot be precluded that mercurous mercury may be an intermediate in the redox transformation of elemental and mercuric mercury or vice versa in the body.

The organic mercury compounds can be divided into mercurials relatively stable versus those rapidly split in the mammalian body. Short chain alkylmercury compounds and diuretic mercurials, pharmaceutically used, which are mainly excreted conjugated or unchanged by the kidneys, belong to the former group.

Among the organic compounds rapidly splitting in the body and of toxicological importance are the phenylmercury compounds and methoxyalkylmercury compounds, both used extensively in pesticides and preservatives. In the following, the toxicology of each mentioned group will be treated independently.

3. Physical and chemical properties

Mercury, Hg, atomic weight 200.6; atomic number 80; density 13.6; melting point -38.9°C; boiling point 356.6°C; crystalline form silver-white metallic liquid; oxidation state 1,2.

Metallic mercury is rather volatile. A saturated atmosphere of mercury vapor contains approximately 18 mg Hg/m^3 at 24°C. Mercury vapor is regarded as insoluble in water. However, at room temperature its solubility is approximately 60 rg/l. Its solubility in lipids is on the order of 5-50 mg/l. In the presence of oxygen, metallic mercury is rapidly oxidized to ionic form. Mercuric salts, like halides, sulfates and nitrates, are water soluble. In aqueous solutions, an equilibrium is established between Hg^0, Hg_2^{2+} (mercurous) and Hg^{++} (mercuric). The representation of the three oxidation stages is determined by the redox potential of the solution and the presence of compounds which can form complexes with the mercuric ions. Mercuric ion Hg^{++} is able to form many stable complexes with biologically important molecules or moities such as sulfhydryl groups. Mercuric mercury forms four different complexes with the chlorine, $HgCl^+$, $HgCl_2$, $HgCl_3^-$, and $HgCl_4^{2-}$ in water. Mercurous mercury is rather unstable in the presence of biological molecules. In the presence of sulfhydryl groups it undergoes disproportionation to one atom of metallic mercury and to one ion of mercuric mercury.

The short chain alkylmercuric compounds form salts with the halogens, which are highly volatile at room temperature, resulting in highly poisonous air concentrations when saturation occurs. The saturation concentration of methylmercury chloride at 20° C is 90,000 mg mercury/m^3 (Swensson and Ulfvarson, 1963). Other salts, such as hydroxide and nitrate of methylmercury, are less volatile and thus less hazardous. Methylmercury dicyandiamide has been used in commercial pesticidal preparations because of its rather low vapor pressure. Methyl- and ethyl - mercury chloride have a high solubility in solvents and lipids. Sulfydryl groups on proteins have a high affinity for the methylmercuric group. Therefore, methylmercury occurs in the organism bound mainly to sulfhydryl groups of large molecules.

Phenylmercury salts and methoxyalkylmercury compounds decompose readily and release mercury vapor.

4. Methods and problems of analysis

Mercury analysis at concentrations found in the environment and in biological material (1-2,000 μg/kg) is complicated, difficult and requires considerable skill and experience on the part of the analyst. Colorimetric, flameless atomic absorption and neutron activation analysis are the three principal types of methods which have gained general recognition.

The colorimetric method is based on the conversion of mercury in the sample to a dithizone complex which is extracted by organic solvents and the amount of dithizonate determined colorimetrically. This method was formerly used extensively, but its not so impressive limit of detection, 0.05 mg/kg in a 0.01 kg sample (Analytic Methods Committee, 1965), and its time-consuming nature are disadvantageous.

Flameless atomic absorption and neutron activation method have replaced the colorimetric methods. The detection limit for atomic absorption is 1-5 ng of Hg. The reported precision, expressed as variation coefficient, is generally better than 20% (Burrows, 1973). The detection limit for neutron activation is 0.1-0.3 μg Hg in a 0.3 g sample; it has high specificity, and the precision in terms of the variation coefficient is better than 10%, as is the accuracy (Westermark and Ljunggren, 1972).

Several interlaboratory comparisons have been published, illustrating the errors encountered in analysis of biological material under controlled practical conditions (Lindstedt and Skerfving, 1972). The greatest errors are probably connected with the collection, storage, transport and handling of the samples, as mercury is volatile and easily lost. Mercury vapor diffuses through plastic materials, adsorbs to surfaces and absorbs into material such as polyethylene, silicone and rubber. In biological material, bacterial activity can reduce mercuric mercury, resulting in the loss of mercury vapor. In aqueous solutions having low concentrations of mercury, mercury tends to adhere to the surface of the collecting vessels.

For determination of mercury in air, mercury can be absorbed in impinger flasks with permanganate, on activated charcoal filters or on other absorbents. Portable monitoring devices have been used for direct determination of mercury in air. In these instruments, the absorption of light emitted from a mercury vapor lamp is measured. These units are, however, subject to the interference of substances such as hydrocarbon solvents often present in the working environment. The presence of strong electromagnetic fields has also been reported to interfere with the result. Reactive tubes, Dräger tubes, have been devised for simple screening (Wolf et al., 1974). Measurement of very low levels of mercury in water requires preconcentration by, for example, dithizone extraction or electrodeposition.

Analysis of mercury in biological material may require oxidative digestion or combustion in oxygen or some kind of extraction. The method must be selected and adapted to the type of material analysed.

Alkylmercury compounds can be identified by thin layer chromatography or gas liquid chromatography. Quantitative analysis of methylmercury is carried out using gas liquid chromatographic techniques after extraction of alkylmercury from the sample with benzene (Westöö, 1966, 1967). As all techniques used involve non-destructive extraction of the alkylmercury from the sample, the recovery has to be checked for every different type of sample matrix as deficiency of extraction of mercury will be determined by both the nature of the sample matrix and the extraction procedures themselves. The detection limit of the method, according to Westöö, is approximately 1-5 µg/kg using a 0.01 kg sample. The precision is 3% at the 0.005 µg level for fish muscle samples. The recovery is generally above 90% but varies with type of sample. Samples such as liver and kidney are more difficult to extract than fish meat.

5. Production and uses

5.1 Production

Mercury occurs in the earth's crust mainly in the form of various sulfides. The red sulfide, cinnabar, is the main content of the mercury-rich ores which are mined, and may contain up to 70% mercury. The world production in 1973 was about 10,000 tons (Korringa and Hagel, 1974). In addition to the pure mercury production, mercury is released into the environment by human activities like combustion of fossil fuels, waste disposal and industrial activities, amounting to about another 10,000 tons per year (Korringa and Hagel, 1974). These figures should be compared with the release of mercury by degassing from the earth's crust and the oceans, estimated to fall between 30,000-150,000 tons per year, 30,000 tons being a minimum figure (Korringa and Hagel, 1974).

Methylmercury is naturally formed in the aquatic environment from elemental mercury and mercuric mercury. The methylation is likely to occur in upper sedimentary layers of sea or lake bottoms (Jensen and Jernelöv, 1967, 1969; Jernelöv, 1968). The methylmercury formed is rapidly taken up by living organisms in the aquatic environment and, by degradation, gases of $(CH_3)_2Hg$ are formed and released into the air (Jensen and Jernelöv, 1968). Dimethylmercury may be decomposed in the atmosphere by acidic rainwater to mono-methylmercury compounds and thereby re-enter the aquatic environment (Jensen and Jernelöv, 1972). It may eventually be demethylated, thereby completing the cycle. Little is known about the quantitative aspects of these cycles. The local load of MeHg may be considerably increased by industrial release of mercuric compounds. This has been shown for mercury release from chemical factories - paper pulp factories and alkaline chlorine factories (Swedish Expert Group, 1971).

5.2 Uses

Of the more than 10,000 tons of mercury produced yearly, 25% is consumed by the chlor-alkali industry, 30% is used in electrical equipment, 15% in paints, 10% in measurement and control systems such as thermometers and sphygmomanometers, 5% in agriculture, 3% in dental practice, and 2% in laboratories. The remaining 20% is divided among military uses as detonators, mercury-containing catalysts, preservatives in the paper pulp industry, pharmaceuticals, cosmetic preparations and others (Korringa and Hagel, 1974). The cytotoxic properties of mercury compounds have given them a widespread usage as germicides and pesticides added to pharmaceuticals, plastics, paints and other products. Methyl- and ethylmercury have seen extensive use in seed treatment. Most industrial countries have banned this use, and the production of alkylmercury compounds has decreased. Phenylmercury acetate has been extensively used as a fungicide and algaecide in paints, plastics and other products. Methoxyethylmercury compounds have replaced the short chain alkylmercury compounds in seed treatment. Under the conditions in which they are used, both types of compounds are unstable and slowly release inorganic mercury.

6. Environmental levels and exposures

6.1 General environment

6.1.1 Food and daily intake

Alkylmercury, formed in the bottom sediment of the ocean and fresh water systems, is enriched to a high degree in the aquatic food chain with the highest levels in the predatory fishes. From the aquatic environment, methylmercury is transformed by species feeding on aquatic organisms to the terrestrial environment. However, enrichment has not been seen to the same extent in the terrestrial food chain. Large tuna fish exceeding 60 kg have levels up to 1 mg/kg of methylmercury in their muscles (Peterson et al., 1973), while terrestrial animals rarely have levels in muscles exceeding 50 µg/kg and generally average 20 µg/kg (Swedish Expert Group, 1971). In areas of polluted water, levels of methylmercury in fish meat may exceed 10 mg/kg, with a tendency to increasing levels with increasing size and age of fishes. Under conditions of agricultural use of alkylmercury, levels of methylmercury in game birds may be raised to toxic levels (Swedish Expert Group, 1971).

A large part of the mercury in food, then, at least in animal products, is likely to be in the form of methylmercury. In fish, the major amount of the mercury is methylmercury. Since the mercury concentration in food products excluding fish varies between a few µg to 50 µg/kg (Bouquiaux, 1974), the daily intake of methylmercury is mainly dependent on the amount of fish consumption and the concentrations of MeHg in consumed fish. Fish consumption may vary between countries, individuals and ethnic groups, which may have a fish consumption of from virtually nothing to 500 g or more per day. The average daily intake of fish flesh in the Swedish population was estimated at 30 g/day (Swedish Expert Group, 1971). This will result in a daily intake of MeHg of between 1-20 µg/day under conditions of consumption of uncontaminated fish. In epidemiological studies on the American Samoan population consuming tuna fish, blood levels have been found indicating a daily intake of between 200-300 µg/day of MeHg (Clarkson et al., 1973). Should the water be polluted, the daily intake from fish consumption can rise to toxic levels as occurred in Minamata and Niigata in Japan, 1953-66 (Swedish Expert Group, 1971). Concentrations of MeHg in fish of 1-20 mg/kg have been reported to result in a maximum daily intake in persons with excessive fish consumption (200-500 g/day) of about 50 mg/day (Swedish Expert Group, 1971).

It should be noted that the daily intake of inorganic mercury will not likely exceed 10 µg/day, from mercury inhalation, intake from drinking water and from food in the absence of occupational exposure. This figure is low in relation to the possible intake of MeHg mentioned above.

6.1.2 Water

Ground water contains between 10-50 ng Hg/l (Dall'Aglio,1968), while surface water in uncontaminated areas may contain up to 200 ng/l (Durum et al., 1970). In rivers draining industrial areas, levels around 1 µg/l may occur (Reichert, 1973). Ocean water contains less mercury, around 30 ng/l (Sillén, 1963). Mercury levels may increase with increasing depth according to Hosohara (1961), who reported a threefold increase from surface to a depth of 3,000 meters.

6.1.3 Ambient air

Mercury concentration in the general atmosphere varies from a few ng/m^3 in remote uncontaminated areas up to around 50 ng/m^3 in urbanised areas (Eriksson, 1967; Williston, 1968). A fraction of the mercury in the atmosphere may be particle-bound. Up to 40 ng/m^3 particle-bound mercury has been reported in the USA in large cities (Goldwater, 1964; Brar et al., 1969). Near areas of industrial emission or areas where mercury fungicides are extensively used, high levels of mercury in the atmosphere have been reported, values on the order of several µg/m^3. From a community close to the mercury mines in Spain, values of 0.8 mg/m^3 have been reported (Fernandez et al., 1966). No conclusive evidence as to what amount of the mercury in water and ambient air is in the form of alkylmercury has yet come forth.

6.2 Working environment

Exposure to mercury vapor is the most common occupational exposure to mercury. Exposure to mercury vapor occurs in a variety of industries such as mercury mining, chlor-alkali factories and instrument manufacturing, as well as laboratories of physics and medicine. Most reports about hazardous exposure come from mining and chlor-alkali industries. Air levels of mercury as high as 5 mg/m^3 have been reported in connection with mining operations. Human exposure is often related to special operations or spillage of mercury compounds on the work clothes from which it evaporates and is inhaled. Although exposure to mercury vapor is the most common exposure with regard to inorganic mercury, mixed exposures to organic mercury compounds in aerosols or mercuric inorganic mercury aerosols occur. In chlor-alkali industries, the presence of chlorine in combination with mercury vapor gives rise to the formation of mercuric chloride aerosols. The handling of mercuric salts in the chemical industry may also cause exposure to aerosols of inorganic mercury.

Exposure to methyl- and ethylmercury has been described in connection with manufacturing and use of these salts in chemical industrial workers and in personnel carrying out seed treatment. Due to the restrictions on the agricultural applications of alkylmercury compounds, occupational exposure is likely to be rare at present in most industrialized countries.

7. Metabolism and toxic effects of elemental mercury and inorganic mercury compounds

There is a considerable difference in metabolism between metallic mercury and mercuric mercury. Due to its lipid solubility, mercury vapor penetrates the membranes of the body and is easily absorbed. On the other hand, the lifetime of mercury vapor in the body is very limited due to the rapid oxidation of elemental mercury to mercuric mercury. The divalent mercuric ion is most likely to bind to sulfhydryl groups on proteins and has limited mobility in the body. As the metabolism and toxic properties of metallic mercury, especially in vapor form, and mercuric mercury differ considerably, they will be treated separately below.

7.1 Elemental mercury

7.1.1 Metabolism

7.1.1.1 Absorption

Inhalation. Mercury vapor is efficiently absorbed from the alveolar air due to the rapid diffusion of mercury vapor through the alveolar membrane (Berlin et al., 1969) and the capacity of red cells to bind and oxidise mercury to mercuric mercury (Clarkson et al., 1961). This process of oxidation can, however, be inhibited by alcohol and aminotriazole (Nielsen-Kudsk, 1965; Magos et al., 1974) whereby the absorption by inhalation is reduced. Considering the effect of dead space, the absorption of mercury vapor at moderate ventilation rates will be about 80% at concentration levels met in the work environment.

Ingestion. Liquid metallic mercury is poorly absorbed from the gastrointestinal tract. Mercury vapor is slowly released from the surface of metallic mercury at a rate which is related to the surface area present. The tendency of metallic mercury to cover itself by mercury sulfide further limits the amount of mercury vapor which can be released. As a result of these factors, the amount of mercury released from metallic mercury ingested is of no toxicological importance. If mercury is broken up into small droplets, the release of mercury will be considerably increased.

Skin. It is likely that mercury can cross the skin barrier but no quantitative data on this are available. It is doubtful whether this route of absorption plays any important role in comparison with inhalation of mercury vapor from a contaminated skin surface.

7.1.1.2 Transport, distribution and biological half-time

It has been shown in mice (Berlin and Johansson, 1964) and in primates (Berlin et al., 1969) that after single exposure to mercury vapor ten times more mercury is retained in the brain than after intravenous injection of the same dose of mercuric mercury. It was suggested (Berlin et al., 1966) that this observation was due to physically dissolved mercury vapor in blood being transported to the brain, or to the release of mercury vapor from blood cells by reduction of ionic mercury bound to the cells. Magos (1968) confirmed the findings of Berlin et al., and showed, by intravenous injection of mercury vapor and by recovering, within 30 sec, 19% of the injected dose in the exhaled air of the animal, that physically dissolved mercury would be enough to explain the uptake of mercury in the brain. It has been shown (Clarkson, 1972) that mercury vapor, in contrast to mercuric mercury, also penetrates the placental barrier, causing an accumulation of mercury in the fetus when the mother is exposed to mercury vapor. Mercury vapor has, however, a limited survival time in the body as it is rapidly oxidized to mercuric mercury in the tissue and behaves then as mercuric mercury. Little is known about steady state distribution during long-term exposure to mercury vapor. Attempts have been made in animal experiments to produce steady state under exposure to mercury vapor. However, the reaching of steady state has not been proved. Berlin (1975) exposed squirrel monkeys to 1 and 2 mg/m^3 of mercury vapor for six hours five days a week for up to two months. They failed to obtain steady state in the brain, although mercury in blood seemed to reach steady state during this time span.

From animal studies (Berlin and Ullberg, 1963; Berlin and Johansson, 1964) with a single exposure to mercury vapor or injection of mercuric mercury salt, it has been shown by autoradiography that mercury is distributed in the mammalian organism specifically to certain types of cells. Mercury has a special affinity for ectodermal and endodermal epithelial cells and glands. Mercuric mercury is thus accumulated in the epithelial lining of the intestinal tract, the squamous epithelium of the skin and hair, in glandular tissues like the salivary glands, thyroid, liver, pancreas, and the sweat glands, and in the kidney as well as epithelial organs, like the testicles and the prostate. These studies have also revealed that the retention time of accumulated mercury varies widely among different organs. Biological half-times vary from a few days to months. The organs with the longest retention times are the brain, kidneys and testicles. These organs are thus likely to show accumulation of mercury at repeated exposure and dominate the distribution at steady state. This has been confirmed in the human brain in cases of occupational exposure to mercury vapor (Takahata et al., 1970; Watanabe, 1971). Little is known about the detailed distribution of mercury in the brain of man or the primates at steady state or after long-term exposure to mercury vapor. Available data from long-term exposure of squirrel monkeys (Berlin et al., 1975) and a few clinical cases of occupational exposure (Takahata et al., 1970; Watanabe, 1971) indicate that mercury is accumulated in the cerebral cortex, especially in the occipital and parietal cortical areas. The evidence from animal experiments is that the detailed distribution in the kidney and other organs accumulating mercury after exposure to mercury vapor, is similar to that seen after exposure to mercuric salts, and will thus be discussed further in section 7.2.1.2.

7.1.1.3 Elimination and excretion

The elimination of mercury after exposure to mercury vapor occurs mainly by excretion of mercuric mercury. However, exhalations of small quantities of mercury vapor have been demonstrated in animals. (Clarkson and Rothstein, 1964) and man (Hursh et al., 1975). It is unclear whether this mercury vapor is a result of reduction of mercuric mercury excreted into the airways or by diffusion of vapor through the alveolar membrane. The routes of excretion of mercuric mercury are via feces, urine, and by salivary, lacrimal and sweat glands. The mechanism and details of renal excretion are discussed in section 7.2.1.3. The rate of excretion is dose-dependent and a considerable species difference has been observed. The best mathematical model seems to be a multicompartmental model with at least 2 or more excretion rates and with one small compartment including the brain with a very long biological half-time (Task Group on Metal Accumulation, 1973). The limited data from human studies indicate that the bulk of mercury is excreted with a biological half-time of about 60 days (Hursh et al., 1975; Piotrowski et al., 1975). Part of the mercury accumulated in the brain is slowly eliminated with a biological half-time which may exceed a year.

7.1.2 Symptoms and signs in poisoning caused by exposure to mercury vapor

7.1.2.1 Acute poisoning

The lung is the critical organ upon acute accidental exposure to high concentrations of mercury vapor. The mercury vapor causes erosive bronchitis and bronchiolitis with interstitial pneumonitis. The patient will eventually succumb in respiratory insufficiency. The symptoms of respiratory distress may be combined with signs caused by effects on the central nervous system, like tremor or increased excitability.

7.1.2.2 Chronic poisoning

Upon long-term exposure to toxic levels of mercury vapor, the central nervous system is the critical organ. Little is known about the pathogenesis of the brain dysfunction seen upon exposure to mercury vapor. With an increasing dose, signs appear which can be characterized as an unspecific, asthenic-vegetative syndrome involving symptoms like weakness, fatigue, anorexia, loss of weight, and disturbance of gastrointestinal functions.

This syndrome has been called micromercurialism (Trachtenberg, 1969; Friberg and Nordberg, 1972). At higher exposure levels, the characteristic mercurial tremor appears as fine trembling of the muscles interrupted by coarse shaking movements every few minutes. It begins in peripheral parts like fingers, eyelids and lips and is intentional. It disappears during sleep. In progressive cases it may develop into a generalised tremor involving the entire body, with violent chronic spasms of the extremities. Parallel to the development of tremor, mercurial erethism develops. This is characterised by severe behavioral and personality changes, increased excitability, loss of memory and insomnia, which may develop into depression. In severe cases, delerium and hallucination may occur.

In addition to the central nervous system signs, cases of severe poisoning may display inflammatory changes of the gums with ptyalism, which may be severe, with salivation of liters per day.

It is still unknown to what degree renal damage may occur in connection with chronic exposure to mercury vapor. Severe nephrotic changes have not been described in patients exposed only to mercury vapor. In patients exposed to a combination of mercury dust and vapor, such changes have been reported (Friberg et al., 1953; Kazantzis et al., 1962). Studies using more refined renal function test methods have not been described with regard to mercury vapor exposure.

7.1.3 Indices of exposure and concentration in the critical organ

Conclusive studies about the relation between levels of exposure to mercury vapor and concentrations in biological media are scarce. It seems, from epidemiological studies (Smith et al., 1970), that mercury concentration in blood may, on a group basis, reflect recent exposure. As mercury concentration in urine is closely related to mercury concentration in blood, urine mercury, on a group basis, may also serve as an index of recent exposure. This is also supported by the results of Smith et al. The variations of urine and blood concentration render these indices useless for diagnostic purposes in individual cases. At present, no index of mercury concentration in the critical organ or in the kidney is known. Under conditions of continuous exposure, animal experiments (Berlin et al., 1975) have shown that levels in blood or urine do not correlate with levels in brain or kidneys as recent exposure is the most important factor determining mercury concentration in blood and urine. (Berlin and Gibson, 1963). Studies on the relation between blood mercury and levels of mercury in the critical organ under conditions of no exposure are still lacking.

7.1.4 Dose-response relationships

Studies on dose-response relationships have been made in which the dose has been determined by the degree of exposure or by absorbed dose as expressed by concentration of mercury in blood or urine. Results from all three approaches will be summarized below. It is, however, uncertain to what extent levels of mercury in air reflect actual exposure. Factors such as the release of mercury vapor from mercury-contaminated clothes, temporary and spot-wise exposure to high levels in connection with special work operations, and variations in physical load that change the rate of lung ventilation limit the value of mercury concentrations in the air as measurements of exposure. Mercury concentrations in blood and urine are influenced by recent exposure and by the body burden of mercury from earlier exposure. The relative contribution of these two parameters determining levels of mercury in blood and urine is still poorly understood. Physiological variation in metabolism also affects the level of mercury in urine.

7.1.4.1 Relation between mercury in air and effect

Data on concentrations of mercury in air necessary to produce acute lung changes are scarce. In one report (Milne et al., 1970), it was reported that an exposure of more than 1-3 mg/m^3 for a few hours caused acute mercurial pneumonitis in four cases. Available epidemiological investigations (Friberg and Nordberg, 1972) indicate that at long-term exposure to mercury concentrations in air of 0.1 mg/m^3 and above, the probability of persons manifesting typical mercurialism with tremor and behavioral changes will increase. At concentrations of 0.1

mg/m^3 and less, the probability of meeting cases of micromercurialism or the asthenic syndrome decreases. There is as yet no substantial accumulation of evidence or any one conclusive report about incidence of poisoning at exposure to concentrations below 0.01 mg/m^3 mercury in air. The prevalence of certain medical findings in relation to mercury exposure in the study by Smith et al. (1970) is shown in Figure 1.

7.1.4.2 Relations between mercury in urine or blood and effects

Although recent exposure to mercury vapor shows a close relation to mercury levels in blood and urine, most epidemiological investigations on exposed populations have not revealed more than a weak association between blood or urinary concentrations of mercury and the occurrence of clinical signs, or the degree of effects, for individual subjects. On a group basis, on the other hand, high levels of mercury in urine and blood may be associated with prolonged exposure to high concentrations of mercury vapor and thus a greater likelihood of occurrence of signs of poisoning. In animal experiments (Berlin and Gibson, 1963) and in epidemiological studies (Benning, 1958; Smith et al., 1970), a close correlation has been shown between levels of mercury in urine and in blood. Levels exceeding 300 µg/liter in urine indicate dangerous exposure but effects may well appear even at lower concentrations (Friberg, 1951; Bidstrup et al., 1951). The level of 300 µg/l in urine corresponds on a group basis to about 100 µg Hg/l in blood (Smith et al., 1970). The association between mercury in blood and in urine and between mercury in air and blood as found in the study by Smith et al. (1970) is seen in Figure 2 and 3, respectively.

7.1.4.3 Relation between mercury in the critical organ and effects

Reliable data on concentrations of mercury in the lung upon acute hazardous exposure to mercury vapor have not been found in the literature. Data on mercury concentration in brain upon exposure to mercury vapor are also scarce. Brigatti (1949) reported concentrations of 6-9 mg/kg in the brain of two persons exposed for several years to mercury vapor, but who died of other causes. Both had shown pronounced signs of mercurialism some years before. Concentrations exceeding 0.5 mg/kg in the brain are not likely to occur in man in the absence of known mercury exposure. The highest reported level (Takahata et al., 1970) of mercury in brain associated with non-fatal mercurialism is 34 mg/kg in the occipital cortex in a person who died of other causes. The highest value published (Takahata et al., 1970) in a person without known signs of classical mercurialism is 18 mg/kg in substantia nigra; the mercury concentration ranged from 5-18 mg/kg in the rest of the brain. In studies on the rabbit (Ashe et al., 1953), a concentration of 1-2 mg/kg was reported to be associated with mild pathological changes in the brain, between 3 and 17 mg/kg with moderate pathological changes and below 0.5 mg/kg no morphological changes were observed. In squirrel monkeys, levels up to 8 mg/kg in the occipital cortex were observed (Berlin, 1975) in the absence of any definite morphological changes in the brain. However, the possibility of behavioral disturbances at these levels could not be precluded.

7.2 Mercuric mercury

7.2.1 Metabolism

7.2.1.1 Absorption

Inhalation. No data are available.

Ingestion. Acute poisoning due to accidental or intentional intake of mercuric chloride was not uncommon at the beginning of this century. Data from reports of such cases (Sollman and Schreiber, 1936) and experimental studies (Rahola et al., 1973) indicate that less than 10% of ingested mercuric chloride can be absorbed. Upon high intake, the corrosive action of mercury chloride may alter the permeability of the gastrointestinal tract, enhancing the absorption.

Skin. It has been demonstrated that upon application of mercuric mercury to the human skin, penetration of mercury occurs, but the mechanism is unknown. Factors such as type and concentration of mercuric compound as well as the condition of the skin determine the rate of absorption (Wahlberg, 1965). In animal studies (Friberg et al., 1961), up to 8% of the mercuric chloride applied to the skin was absorbed in 5 hours. The available data are insufficient for evaluating the importance of skin absorption relative to absorption by inhalation under conditions of occupational or pharmaceutical exposure.

7.2.1.2 Transport and distribution

Mercuric mercury is divided in blood between erythrocytes and plasma in about equal amounts (or more in plasma). In the erythrocytes, mercury is probably to a large extent bound to sulfhydryl groups on the hemoglobin molecule. In plasma, mercury binds to sulfhydryl groups on plasma proteins. The distribution between different plasma protein fractions varies with dose and time after administration. Mercuric mercury does not readily cross the blood-brain barrier or the placental barrier. The rate of uptake from blood in different organs varies widely, as does the rate of elimination from different organs. The distribution of mercury within the body and within organs will thus vary widely with dose and time lapse after absorption. So far, no one has attempted to describe the steady state distribution. The distribution of Hg^{2+} in the body is highly differentiated to specific organs and, within the organs, to specific cells. This is likely to be related to the occurrence of ligands with affinity to mercury. Under all conditions, however, the dominating mercury pool in the body is the kidney. In view of animal data, other organs or cells where mercury is likely to accumulate are the liver, the mucous membranes of the intestinal tract, and the epithelium of the skin, the spleen, the interstitial cells of the testicles, and some parts of the brain. In animal experiments, the placenta and fetal membranes have also been observed to accumulate and retain mercury (Berlin and Ullberg, 1963).

In the kidney, most mercury is found in the renal tubules (Taugner, 1966; Taugner et al., 1966). In the liver, the highest concentration is seen in the peripheral part of the liver lobule around the bile ducts (Berlin and Ullberg, 1963). In the brain, most mercury is seen in gray matter, more in some nuclei in the brain stem and some parts of the cerebellum (Nordberg and Serenius, 1969; Berlin et al., 1969).

7.2.1.3 Excretion

As has been mentioned in section 7.1.1.3, mercuric mercury is excreted by the kidney, by the fecal route, by sweat glands, lacrimal glands and mammary glands, and by salivary glands. The major part of absorbed mercuric mercury is excreted in urine and feces. Partition between these two routes is dose-dependent and data indicate a larger fraction excreted by urine upon administration of higher doses.

Little is known about the mechanism behind mercury excretion in the intestinal tract. Except for the excretion by saliva, mercury is excreted by the liver through the bile and also by the mucous membranes of the small intestines and colon. Nor is the mechanism of urinary excretion of mercury known. It is still uncertain whether small amounts of mercury are filtered through the glomerular membranes. The evidence is that less than 1% of the mercury in the plasma is in ultrafiltrable form. To what extent a small fraction is filtered remains a subject of conflicting reports. The major part of the mercury in the kidney is taken up from the blood and stored in the kidney, a process not necessarily linked to the process of excretion. Animal experimental data indicate that excretion is more correlated to blood concentration of mercury than to the mercury load in the kidney (Berlin and Gibson, 1963). Transfer of mercuric mercury through the proximal tubules has been demonstrated in the avian kidney (Vostal and Heller, 1968). Most experimental data from mammals point to some kind of transfer of mercury through the tubular wall. Some authors have reported the existence of a protein water-soluble component in the kidney with high affinity to mercury and increasing in the presence of mercury exposure (Piotrowski et al., 1974). Others have reported the binding of mercury to glutathione in the kidney (Richardson and Murphy, 1975).

The total excretory capacity of the body is illustrated by the elimination rate from the whole body. It has been demonstrated in rats (Rothstein and Hayes, 1960) that the elimination curve is best described as a multi-phasic exponential curve, having a rapid phase with a half-time of about 5 days, another phase with a half-time of about a month and still another with a half-time of about 3 months. Experimental studies do not contradict a similar human elimination pattern, although only the more rapid phases have been followed thus far. Rahola et al. (1971) found a half-time of 42 days for 80% of the absorbed amount after an oral tracer dose in man. The half-time of the remaining 20% could not be determined.

7.2.2 Symptoms and signs in poisoning due to mercuric salts

7.2.2.1 Acute poisoning

Upon accidental or suicidal ingestion of sublimate or other mercuric salts, the critical organs are the kidney and the intestinal tract. The corrosive effect of concentrated mercuric salt solution on the mucous membranes of the gastrointestinal tract causes extensive precipitation of proteins. Gastric pain and vomiting may ensue. If the salt is allowed to pass farther down, general abdominal pain and bloody diarrhea, with necrosis of the intestinal mucosa, will occur. This may lead to circulatory collapse and death. If the patient survives the gastrointestinal damage, the critical organ will be the kidney. Within 24 hours, renal failure due to necrosis of the proximal tubular epithelium, which develops into anuria and uremia, occurs. A part of the mechanism behind the tubular necrosis may a local vasospasm.

7.2.2.2 Chronic poisoning

Chronic poisoning due exclusively to mercuric mercury salts is unlikely. Most chronic exposure involves a mixture of mercury vapor and mercuric mercury. Renal damage with nephrotic syndromes has been described in such mixed exposures. It is possible that exposure to mercuric mercury is the main cause of those signs since the kidney is the critical organ in prolonged exposure to mercuric mercury in animals (Skerfving and Vostal, 1972). Other signs which may be expected are increased salivation, inflammatory changes of the gums and black lines on the gums.

Mercuric compounds locally applied to the skin may cause idiosyncratic skin symptoms like erythema and more severe exfoliative dermatitis, involving the whole body. A specific form of hypersensitivity is seen in children between 4 months and 4 years of age. This syndrome, called acrodynia or pink disease, is characterized by a general rash over the body. Other symptoms are chills, swelling and irritation of the hands, feet, cheeks and nose, usually followed by desquamation, loss of hair and ulceration. In addition to the skin symptoms, the disease features irritability, photophobia, sleeplessness and profuse perspiration, which may lead to dehydration. The perspiration is accompanied by dilated and enlarged sweat glands and desquamation of the soles and palms. Hyperplasia and hyperkeratosis of the skin in the peripheral parts of the extremities are seen. If mercury exposure is eliminated, the signs disappear gradually. Acrodynia cases of mercury etiology usually show increased levels of mercury in urine (>50 µg/l) (Warkany and Hubbard, 1948,1951,1953).

7.2.3 Diagnostic indices of exposure, body burden and concentration in critical organ

There are no data available relating concentrations of mercury in blood and urine to data on exposure and absorption of mercuric mercury. From theoretical considerations, it can be assumed that, as is the case for exposure to mercury vapor, concentration of mercury in blood and urine may, on a group basis, be related to the degree of absorption of or the exposure to mercuric mercury. Renal biopsy has been used as a diagnostic procedure to discover mercury concentration in the critical organ (Kazantzis et al., 1962).

7.2.4 Dose-effect and dose-response relationships upon exposure to mercuric salts

Data on dose-effect and dose-response relationships upon exposure to mercuric salts are scarce. The lethal dose upon acute poisoning is on the order of 1 g, judging from old clinical reports about suicide cases. Severe poisoning has been reported after ingestion of less than 1 g. Some data are available on the relation between concentration of mercury in the kidney and kidney damage. In persons not exposed to mercuric mercury in addition to the daily intake by food, water and air, the mercury concentration in the kidney can be expected to range between less than 0.1 mg/kg and 3 mg/kg (Berlin, 1972). In cases of poisoning due to mercuric salts, 10-70 mg/kg mercury in the kidney has been reported (Clennar and Lederer, 1958;

Kazantzis et al., 1962). These values tally with the concentrations seen in kidneys of mercury-poisoned rats (Ashe et al., 1953).

8. Metabolism and toxic effects of organic mercury compounds

8.1 Organic compounds relatively stable in the mammalian body

Organic mercury compounds which resist chemical degradation by the biochemical processes in the body are the short chain alkyl compounds and some mercurials used in pharmaceutical practice. Among the alkyl compounds, methylmercury compounds occur naturally and it is to them that most accumulated knowledge pertains. Available data indicate that ethylmercury compounds have toxicological properties similar to those of the methylmercury compounds. This presentation will therefore be limited to methylmercury compounds, which will be abbreviated to MeHg. For the toxicology of the organic mercury compounds used for pharmaceutical purposes, the reader is referred to handbooks on toxicology (e.g. Goodman and Gilman, 1970).

8.1.1 Metabolism

8.1.1.1 Absorption

Inhalation. MeHg compounds can be absorbed by inhalation. Vapors of MeHg salts easily penetrate the membranes of the lung and the absorption rate can be estimated at around 80%. In cases of exposure to alkylmercury salt aerosols, the absorption rate would be dependent on particle size and the rate of deposition in the respiratory tract.

Ingestion and skin. MeHg ingested with food or ingested in connection with food is likely to be bound to proteins in the intestinal tract. It is efficiently absorbed through the intestinal tract in experiments on man (Åberg et al., 1969; Miettinen, 1973) and primates (Berlin et al., 1975).

Absorption of alkylmercury compounds by the skin is likely to occur. The rate will be dependent on the type of compound, the concentration and the condition of the skin. Friberg et al. (1961) and Wahlberg (1965) have demonstrated skin absorption of an aqueous solution of MeHg in guinea pigs. Cases of poisoning due to local application of MeHg-containing ointment to the skin have been described (Suzuki et al., 1970). To what extent the absorption can be explained by inhalation cannot be estimated from the reports.

8.1.1.2 Transport and distribution

MeHg absorbed into the body is bound to protein sulfhydryl groups or, to a lesser extent, to sulfhydryl groups of amino acids,or peptides,like cysteine and glutathione. Thus, in blood plasma, MeHg is bound to plasma proteins mainly and transported through the cell walls by some unknown mechanism. In the blood, MeHg is accumulated to a large extent - more than 90% - in the red cells. MeHg is slowly distributed from the blood to the organism. Equilibrium between blood and body is not reached until after four days in the monkey (Berlin et al., 1975). The adult brain and the fetal brain show a special affinity for MeHg in squirrel monkeys, with levels of alkylmercury at least 3-6 times higher in brain than in blood, depending on dose (Berlin et al., 1975). In studies of the distribution of MeHg after tracer doses of radioactively labeled MeHg in man, Åberg et al. (1969) found 10% of the body burden of MeHg in the head. Miettinen (1973) found about 1% in one liter of blood. These values correspond to about six times higher MeHg concentrations in brain than in blood. The uptake in brain is slower than in other organs as has been demonstrated in the mouse (Berlin and Ullberg, 1963). In the rest of the body, MeHg is rather evenly distributed in the tissues compared to other mercury compounds, with an intercellular distribution. MeHg undergoes biotransformation to inorganic mercury by demethylation in the body, the mechanism of which is still unknown. Considerable levels of inorganic mercury have been demonstrated in kidney, liver, feces, bile and urine after administration of MeHg in primates (Berlin et al., 1975). Biotransformation is unlikely to occur in the brain as more than about 95% of mercury in brain has been demonstrated to be in the form of MeHg upon exposure to MeHg. The distribution in the fetus is close to that of the mother, although fetal brain levels of mercury may be higher (Berlin and Ullberg, 1963).

8.1.1.3 Elimination and excretion

The main routes of elimination of MeHg are via the liver into bile and via the kidney into urine. The net excretion in humans amounts to about 1% of the body burden, corresponding to a biological half-time of 70 days, when this burden is non-toxic (Swedish Expert Group, 1971). Clinical observations from MeHg poisoning epidemics in Japan (Swedish Expert Group, 1971) and Iraq (Bakir et al., 1973) support an elimination in man under conditions of intoxication of the same order of magnitude. The major part of the excretion is by the fecal route. Much of the MeHg excreted in the bile is absorbed in the gut, producing an enterohepatic circulation of MeHg. However, a part of the mercury in bile - about 30-80% - in the monkey (Berlin et al., 1975) is inorganic mercury, derived from the demethylation of MeHg in the body. This part, less effectively absorbed in the gut, is excreted. The relative amount of inorganic mercury in bile may be dose-dependent. About 90% of the total excretion of MeHg in man is by the fecal route. MeHg is also excreted in breast milk, the concentration being about 5% of the concentration in the maternal blood (Skerfving, 1973; Bakir et al., 1973). 20% of the mercury in breast milk is MeHg provided the load of MeHg is non-toxic (Skerfving, 1973). Bakir et al. (1973) reported 60% MeHg in Iraqi cases of MeHg poisoning; thus, the fraction of MeHg may be dose-dependent.

The capacity for MeHg elimination varies in the population. Analyses of consecutive hair segments from MeHg exposed populations in Iraq (Al-Shahristani and Shihab, 1974) suggest that a part (10%) of the population eliminates MeHg at a rate considerably less (biological half-time 110-190 days) than 1% per day. Whether this may be due to the existence of genetic enzyme anomalies in the population or to other causes is as yet unknown.

8.1.2 Symptoms and signs in poisoning caused by exposure to alkylmercury

Available data point to great similarities in symptoms and signs of poisoning due to ethyl mercury and MeHg. Most detailed information has to do with MeHg. There is no sharp difference between acute and chronic poisoning from exposure to MeHg compounds. Once a toxic dose has been absorbed in the body, it is retained for a long time, causing functional disturbances and damage. On the other hand, a single toxic dose does not produce signs or symptoms until after a latency period, which may vary from one to several weeks. Signs and symptoms from poisoning due to MeHg show large species differences, mainly due to differences in rate of excretion and distribution. Two clinical types of intoxication may be discerned, a prenatal and a postnatal type. These give rise to different kinds of signs and symptoms.

8.1.2.1 Prenatal poisoning

The clinical picture in prenatal MeHg poisoning is that of an unspecific infantile cerebral palsy (Swedish Expert Group, 1971), involving ataxic motor disturbances and mental symptoms. Upon autopsy, the brain is found to be hypoplastic with a symmetrical atrophy of cerebrum and cerebellum. Decreased numbers of neurons and distortion of the cytoarchitecture in the cortical areas are histological features. The changes coincide with those of cerebral palsy of unknown etiology. Similar findings have been reported in cases of ethylmercury poisoning (Bakulina, 1968).

8.1.2.2 Postnatal poisoning

The clinical signs of postnatal intoxication due to MeHg are characterized by sensory disturbances with paresthesia in the distal extremities, in the tongue and around the lips. These are early signs, occurring with light intoxication. In more severe intoxication, ataxia, concentric constriction of the visual fields, impairment of hearing and extrapyramidal symptoms may appear. In severe cases, clonic seizures have been observed. The pathological changes in the central nervous system are characterized by general neuron degeneration in the cerebral cortex with gliosis, most pronounced in the calcarine, the precentral and postcentral areas. These changes are accompanied by atrophy of the cerebral cortex. In the cerebellar cortex, a loss of granular cells is engendered, also leading to atrophy.

8.1.3 Indices of exposure and concentration in the critical organ

Experimental studies in man and primates have shown that mercury concentration in blood is linearly correlated to intake of MeHg and to the concentration of MeHg in the critical organ, the brain, at non-toxic body burdens. As more than 90% of MeHg in blood is to be found in the erythrocytes, mercury concentration in red cells is the most reliable index of MeHg body burden and brain concentration.

MeHg is deposited in the hair at the formation of the pile. The deposition of MeHg in the pile is proportional to the mercury concentration in blood at the time of pile formation. Thus the mercury concentration in the hair pile constitutes a calendar of mercury concentrations in blood, which have occurred during the formation of the pile. MeHg concentration in the hair can be used as an index of mercury concentration in blood, in the critical organ, or body burden of mercury, provided that allowance is made for the growth rate of the hair pile, about 1 cm a month, and the time lag between hair formation and extrusion. Under occupational conditions, the possibility of external hair contamination should be kept in mind.

As urinary excretion of MeHg is very small, MeHg concentration in urine is easily masked by the inorganic mercury present. Thus, urine concentration of MeHg is not a good index of MeHg body burden or of MeHg concentration in the critical organ.

Under steady state conditions, the quotient between hair levels and blood levels of MeHg is around 250 (Skerfving, 1974; Tonkelaar et al., 1974).

8.1.4 Dose-response relationships

Most of our knowledge about dose-response relationships in MeHg poisoning is derived from studies of the epidemics of MeHg poisoning in Iraq (Bakir et al., 1973) and Japan (Swedish Expert Group, 1971), and studies on populations eating mercury-contaminated fish (Skerfving, 1973; Clarkson et al., 1973). When considering the dose-response relationships in MeHg poisoning, three main effects can be discussed - the neurotoxic effect, the embryotoxic effect, and the genetic effect as shown in chromosomal aberrations of the lymphocytes. The dose-response relation for each of these effects will be discussed separately below.

The dose of MeHg can be expressed in terms of level of intake, amount absorbed as reflected by concentration of MeHg in blood or hair, and finally in terms of concentration in the critical organ, the brain. Each approach will be used below for each effect whenever data are available.

8.1.4.1 Incidence of signs and symptoms related to intake or body burden of MeHg

Assuming a 70-day half-time for MeHg, Bakir et al. (1973) estimated the body burden of MeHg causing a 5% risk of paresthesia. They used data from 58 persons who had consumed a known amount of bread containing MeHg. They arrived at the figure of 0.5-0.8 mg/kg body weight. The body burden corresponding to a 5% mortality risk was about 10 times higher. However, little is known about the biological half-time for MeHg at toxic dose levels. It may be longer than assumed. In a survey of 926 persons from heavily affected villages in Iraq (Al-Mufti et al., 1974), 427 persons known to have consumed MeHg-contaminated bread were selected, and the frequency of paresthesia was reported for different cohorts with different intakes of MeHg. An estimate of the body burden corresponding to the 5% risk of paresthesia based on these data tallies well with the data of Bakir et al. (1973).

8.1.4.2 Incidence of signs and symptoms of MeHg poisoning related to concentration of MeHg in blood

A thorough review of data from Japanese epidemics of MeHg poisoning by a Swedish Expert Group (1971) resulted in the conclusion that the lowest blood level connected with signs of MeHg poisoning reported in Japan is around 200 µg/l. Insufficient numbers of victims were subjected to blood analysis to allow an estimate of risk at that level. Bakir et al. (1973) reported blood values in an exposed population in Iraq 65 days after cessation of exposure. They also reported the frequency of signs of different cohorts with different levels of blood concentration of MeHg. An estimate of the blood concentration of MeHg - assuming a log-linear relation between incidence rate and MeHg in blood - corresponding to a 5% risk in this population, gives a value for blood concentration between 200 and 300 µg/l 65 days after cessation of exposure.

8.1.4.3 Incidence of signs and symptoms of MeHg poisoning related to concentration of MeHg in hair

The lowest mercury concentration found in hair in connection with symptoms in the Niigata epidemic of MeHg poisoning was 50 mg/kg The available data indicate that the risk at this level is less than 10% and possibly not greater than 5%.

In a study on 843 exposed persons in the Iraqi epidemic of MeHg poisoning, the lowest hair value associated with symptoms or signs was 120 mg/kg (Al-Shahristani et al., 1974). The data do not permit any calculation of risk at this level of hair concentration.

8.1.4.4 Incidence of signs and symptoms of MeHg poisoning related to concentration of MeHg in the brain

Few data on concentrations of MeHg in the brains of fatalities from the epidemic in Japan have been reported. Almost no data are available from the extensive epidemic in Iraq. The lowest data reported from Japan (Swedish Expert Group, 1971) are on the order of 5 mg/kg in brain tissue. This value can be estimated to correspond to about 800 µg/l in blood, 200 mg/kg in hair. These values are rather low in comparison with dose-response levels for early signs like paresthesia. No basis for estimation of mortality rate exists at this level.

8.1.5 The embryotoxic effect

In the Minamata epidemic of MeHg poisoning, 23 cases of prenatal intoxication were encountered. A larger number probably occurred in the Iraqi epidemic. Among the Japanese cases, the mothers of the affected children had commonly shown no clinical signs of poisoning. Scanty data available on mercury levels in biological materials like blood and hair (Swedish Expert Group, 1971) indicate that the difference in sensitivity between the fetus and the adult organism is less than a factor of 5 and closer to a factor of 2. The report from the Iraqi epidemic supports this estimate (Amin-Zaki et al., 1974a). The data do not permit the estimation of a dose-response relationship for this effect.

8.1.6 The genetic effect

Although MeHg has been proved mutagenic under experimental conditions (Ramel, 1972), little evidence of such an effect is available from clinical experience. Skerfving et al. (1974) reported dose-related chromosome aberrations in lymphocytes of consumers of MeHg-contaminated fish. They found such aberrations at blood MeHg levels of around 100 µg/l. However, studies on intoxicated persons in the Iraqi epidemic have not revealed any greater incidence of chromosomal aberrations compared to a control population (Baghdad meeting, 1974).

8.2 Organic mercuric compounds unstable in the mammalian body

There are two main mercurials of practical importance which belong to the group of organic mercury compounds unstable in the mammalian organism - the phenylmercury compounds and the alkoxyalkylmercury compounds, chiefly the methoxyethylmercury compounds.

8.2.1 Metabolism

8.2.1.1 Absorption

Ingestion. Animal experiments indicate that phenyl Hg salts are absorbed more efficiently than mercuric salts in the gastrointestinal tract (Prickett et al., 1950). There are no data on the absorption of phenyl Hg salts or alkoxyalkyl Hg compounds after ingestion in man.

Inhalation. Both phenyl Hg compounds and alkylalkoxy Hg compounds are absorbed via inhalation of aerosols (Hagen, 1955). Determining factors for the degree of absorption will be particle size and solubility of the salt aerosolized.

Skin. There is clinical evidence that phenyl Hg compounds applied on the skin (Biskind, 1935) or locally in the vagina (Eastman and Scott, 1944) are absorbed. Data are not sufficient for any quantitative conclusions. No data are available on the skin absorption of methoxyethyl Hg compounds.

8.2.1.2 Transport and biotransformation

The phenyl Hg and methoxyethyl Hg compounds are decomposed, mainly in the liver, to inorganic mercury (Daniel et al., 1971, 1972; Gage, 1975). Experimental evidence indicates that the rate of biotransformation of methoxyethyl Hg is more rapid than that of phenyl Hg. Most organic mercury is transformed to mercuric inorganic mercury, within 24 hr in the case of methoxyethyl Hg and within the first four days in the case of phenyl Hg compounds in the rat. Phenyl Hg evidently penetrates cell membranes more easily than Hg^{2+}. Thus, about 90% of phenyl Hg in blood is found in the red cells (Berlin, 1963; Goldwater et al., 1964). However, neither phenyl Hg nor methoxyethyl Hg is transferred through the blood-brain barrier or the placental barriur to a larger extent than Hg^{2+} (Ulfvarsson, 1962; Berlin and Ullberg, 1963).

8.2.1.3 Distribution

Mercury distribution after long-term exposure to phenyl Hg or methoxyalkyl Hg is likely to be close to distribution after Hg^{2+} exposure. However, in the case of phenyl Hg, one important difference should be emphasized. As recent exposure determines the mercury level in blood, under conditions of exposure to phenyl Hg, a large fraction of the mercury in blood will be found in the red cells in contrast to what can be expected in exposure to mercuric mercury (Goldwater et al., 1964).

8.2.1.4 Excretion

Judging from animal experiments, phenyl Hg may be more efficiently excreted by the liver in bile than Hg^{2+}. It is unclear to what extent methoxyethyl mercury is excreted unchanged. Conclusive data from observations in humans are not available for either phenyl Hg or methoxyethyl Hg.

8.2.2 Indices of exposure or concentration in critical organs

Occupational exposure to phenyl Hg compounds or methoxyethyl Hg compounds is likely to be a mixed exposure due to the instability of these mercurials. Indices generally useful for evaluating exposure levels or body burden of mercury will be difficult to find. Reports from Goldwater et al. (1964), however, suggest that under similar exposure conditions mercury levels in urine and blood may be indicative of levels of exposure to phenyl Hg compounds.

8.2.3 Signs and symptoms due to poisoning by phenyl Hg compounds and methoxyethyl Hg compounds

Both types of compounds may cause local damage in the lung from inhalation or on the skin from contact with concentrated solutions. Sensitization has been described for phenyl Hg compounds in single cases (reviewed by Nordberg and Skerfving, 1972). Cases of intoxication due to long-term exposure are few and the reports are conclusive to a limited degree as to type of exposure and dose absorbed. There is no clear evidence that the clinical pattern deviates from that expected for intoxication by mercuric salts. The higher level of mercury in the liver seen in animal experiments after exposure to phenyl Hg compared to inorganic mercury salts may tally with the observations described by Cotter (1947). This author found liver damage in ten subjects exposed to phenyl Hg salts. Other substances may also have been involved, however. Renal damage and intestinal complaints have been reported upon intoxication due to phenyl Hg compounds and methoxyethyl Hg compounds (reviewed by Skerfving and Vostal, 1972).

8.2.4 Dose-response relationships

The quantitative data available do not permit extensive conclusions about dose-response relationships in exposure to phenyl Hg or methoxyethyl Hg compounds. However, available clinical reports, especially those concerning phenyl Hg poisoning, suggest that these compounds are not more toxic than mercuric salts in long-term exposure, but rather less toxic.

9. Prognosis and treatment of intoxication due to mercury compounds

The prognosis of poisoning due to mercury compounds is dependent on the type of mercury compound involved and the dose. All specific therapy is aimed at lowering the concentration of mercury at the site of action in the organism and to remove the mercury compound from the organism. This can be achieved by different methods common to all kinds of mercury poisoning. In all severe cases, the first choice should be hemodialysis and infusion of chelating agents for mercury, such as cysteine or N-acetyl penicillamine. In less severe cases, mobilization and redistribution of mercury can be achieved by aid of chelating agents such as BAL (dimercaptopropanol) and N-acetyl penicillamine. These methods can only be used in selected cases and not in all types of mercury compounds. The excretion of mercury can be increased by surgical establishment of gall bladder drainage, thereby breaking the enterohepatic circulation of mercury. This method is most efficient with regard to those types of compounds for which enterohepatic circulation plays an important role.

9.1 Mercury vapor

The prognosis in pronounced intoxication by mercury vapor involving severe tremor and mental changes is, according to the literature, remarkably good with complete regression if exposure ceases. Whether the regression is due to a compensatory mechanism - remaining neurons taking over the function of damaged ones - or is a complete regression is not possible to answer with present knowledge, nor is it known whether mercury deposited in the brain can be mobilized by therapeutic measures, or whether regression is due to mercury eliminated from the brain or converted to and deposited in an inert form.

9.2 Inorganic mercuric mercury

Severe sublimate poisoning with renal tubular damage is a fatal condition, but this prognosis can be considerably improved by therapeutic measures. In acute poisoning, BAL (dimercaptopropanol) will efficiently mobilize mercury from the kidney and redistribute it in the body (Berlin and Lewander, 1965). It should therefore be used in this kind of poisoning in combination with hemodialysis with cysteine infusion to remove the mercury from the body. The experimental evidence is that the damaged tubules can regenerate to a considerable degree.

9.3 Short chain alkyl Hg

Signs and symptoms of intoxication with alkyl Hg compounds do not appear until several weeks after absorption. Moreover, the appearance of signs of intoxication is secondary to severe damage of the cerebral cortex. If exposure is stopped, considerable regression of signs and symptoms may occur according to the experiences in the Iraqi epidemic (Damluji et al., 1974). To date, therapeutic improvement of the prognosis upon manifest intoxication has not been seen clinically. Good experimental and clinical evidence shows that hemodialysis with cysteine infusion can drastically reduce the concentration of alkyl Hg in the brain and the body (Kostyniak et al., 1974, 1975; Al-Abassi et al., 1974). This therapy should be the first choice in any progressive state of intoxication. This treatment can be followed by continuous therapy with N-acetyl penicillamine to reduce the body burden of alkyl Hg further (Shapiro et al., 1973). If hemodialysis cannot be applied, gall bladder drainage is a must, with oral replacement of the bile salts and electrolytes lost in the drain.

9.4 Phenyl Hg compounds or methoxyethyl Hg compounds

Severe renal damage due to these types of compounds should be treated with hemodialysis. BAL is contraindicated as it forms lipid soluble complexes with the organic mercury compounds and redistributes to the brain whereby it may cause severe disturbance in the central nervous system. In cases of acrodynia or pink disease, N-acetyl penicillamine should be used for mobilisation of mercury from the body.

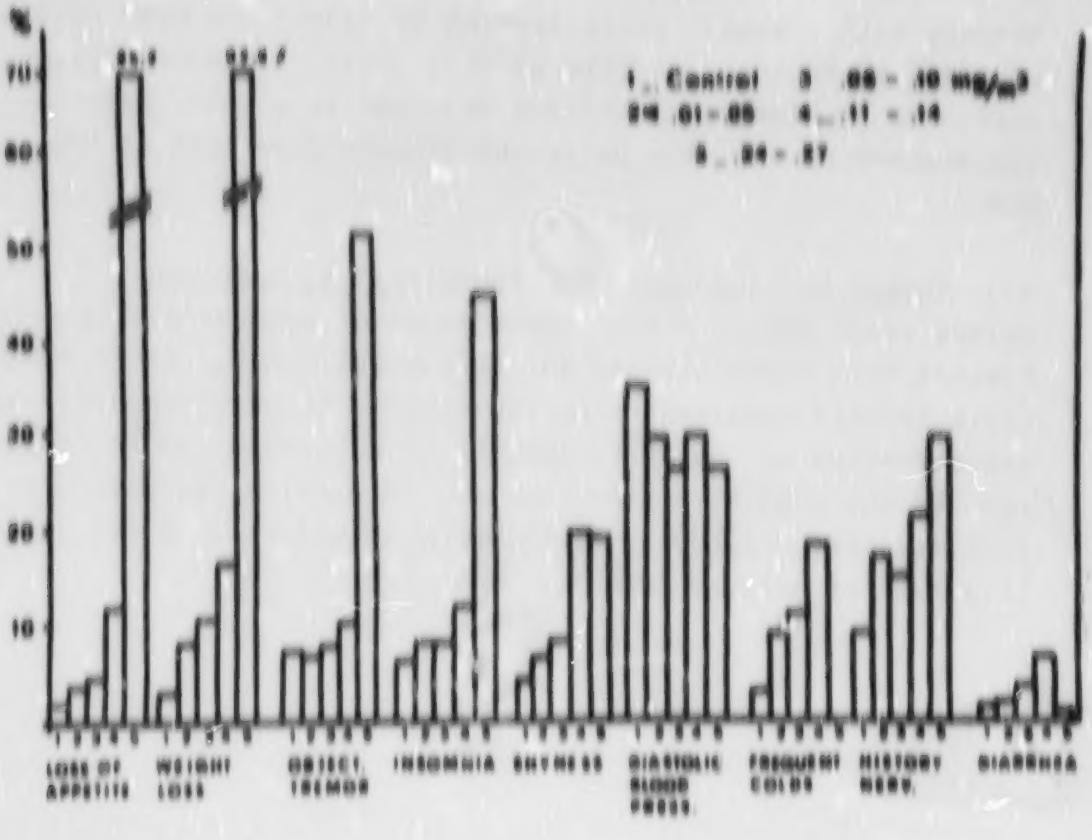

Figure 1. Percentage prevalence of certain signs and symptoms among workers exposed to mercury in relation to degree of exposure (From Smith et al., 1970). Data on diastolic blood pressure probably mean % below a certain level. This level is not given in the article.

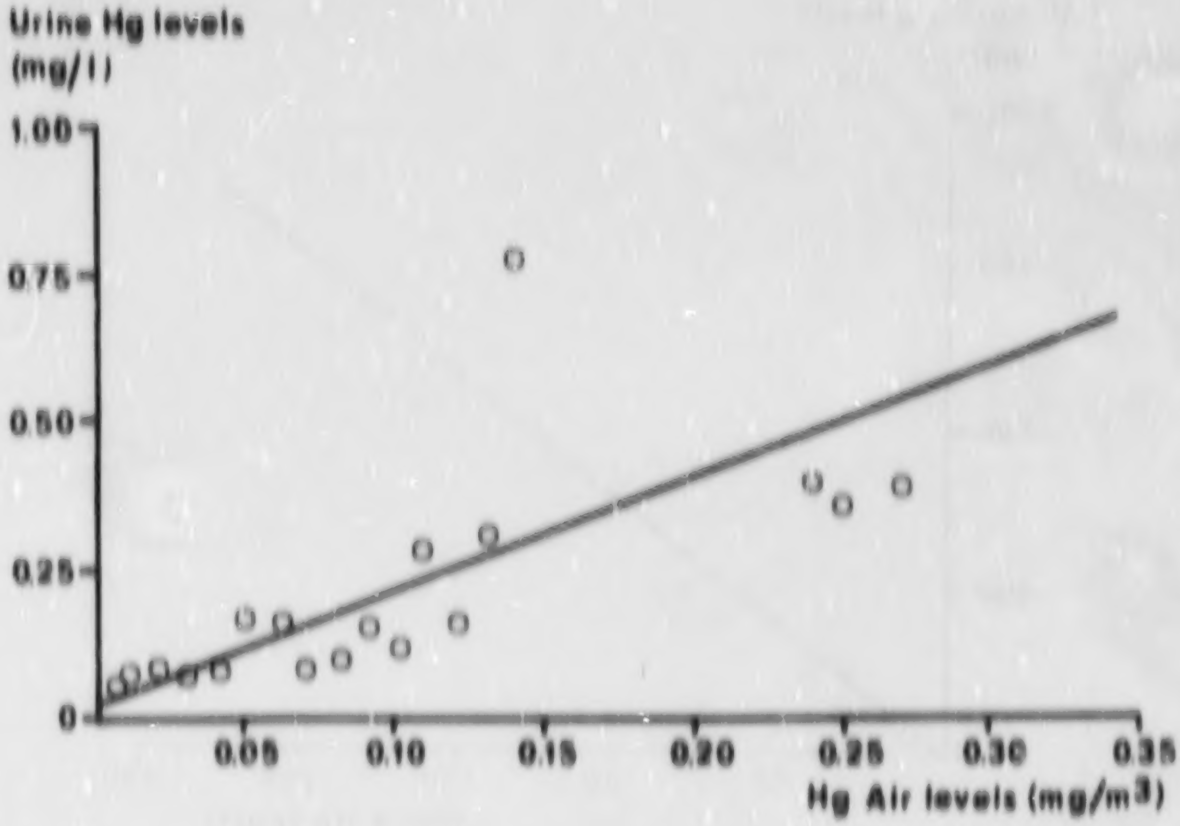

Figure 2. Concentrations of mercury in urine (uncorrected for specific gravity) in relation to time-weighted average exposure levels (From Smith et al., 1970).

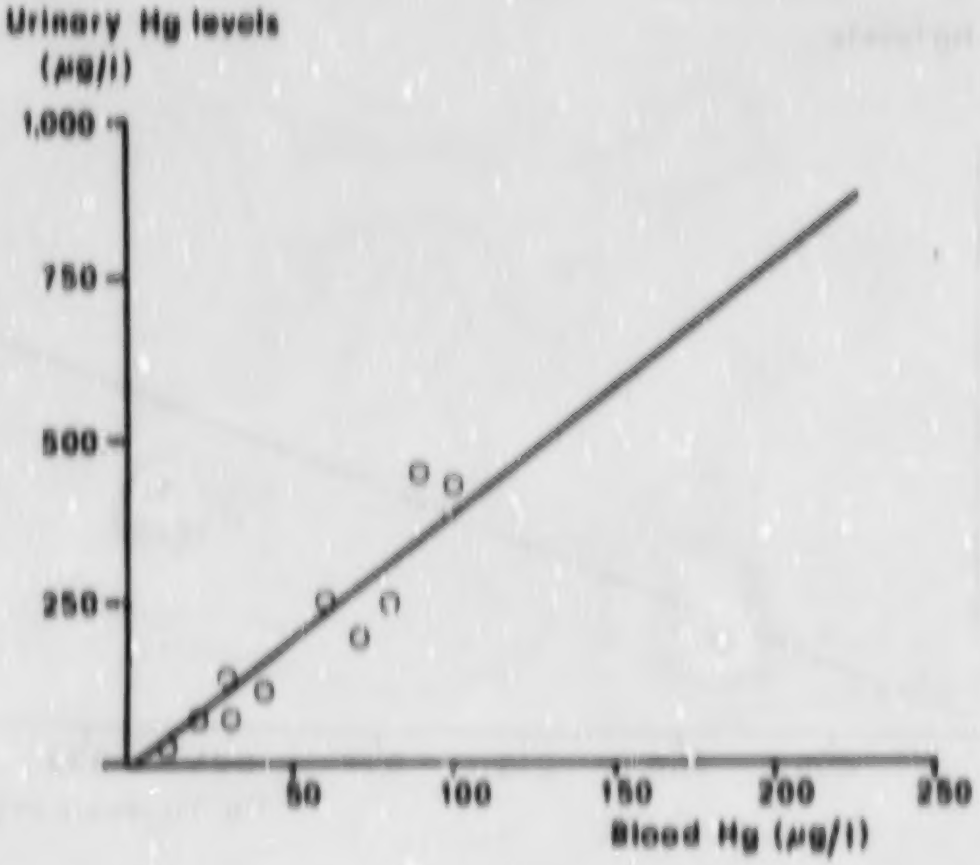

Figure 3. Relationship of concentrations of mercury in blood and in urine (uncorrected for specific gravity) (From Smith et al., 1970).

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MOLYBDENUM

Lars Friberg

1. Abstract

Soluble molybdenum compounds are readily absorbed via ingestion and inhalation. The highest molybdenum concentrations are found in kidney, liver and bones. The excretion, primarily via the urine, is rapid. The biological half-time is probably from a few hours in small laboratory animals up to a couple of weeks in humans.

Molybdenum is an essential element. Its metabolism is related to copper and sulfur metabolism. Copper generally has a beneficial effect on the symptoms caused by excessive molybdenum, but the action of sulfur compounds, especially sulfate, is not so clearly understood. Both positive and negative effects have been reported, depending upon the copper status.

In livestock chronic molybdenum poisoning known as "teart disease" is caused by a diet high in molybdenum and low in copper. Symptoms include anemia, gastrointestinal disturbances, bone disorders and growth retardation. In laboratory animals excessive molybdenum may give rise to morphological and functional changes in the liver, kidneys and spleen. It has a growth depressive action and deformities of bone may occur.

A few cases of pneumoconiosis have been reported among workers exposed to metallic molybdenum and molybdenum trioxide. Increased blood uric acid values and gout-like symptoms have been reported among workers exposed to molybdenum in a copper-molybdenum plant as well as among the general population living in an area with high molybdenum and low copper content in soil and vegetables.

A review on the transport and biological effects of molybdenum has been made by the Molybdenum Project (1974) and a general review on molybdenum has been given by Friberg et al. (1975).

2. Physical and chemical properties

Molybdenum, Mo, atomic weight 95.9; atomic number 42; density 10.2 (20°); melting point 2617°C; boiling point 4612°C; crystalline form silver-white metal or gray-black powder, cubic; oxidation state 2,3,4?,5?,6.

More than 50 inorganic forms of molybdenum are known and organometallic forms also exist. Inorganic compounds to be mentioned in this chapter are ammonium molybdate, calcium molybdate, molybdic oxide, sodium molybdate, molybdenum disulfide and molybdenum trioxide.

3. Methods and problems of analysis

Colorimetric methods, among them the thiocyanate and the dithiol methods, have been used for decades for the determination of molybdenum. During later years neutron activation, atomic absorption and X-ray fluorescence have been widely employed. For detailed discussion on the determination of molybdenum reference is made to reviews by Meglen and Glaze (1973, 1974). Duval (1971) in a comparison of different methods found detection limits for the thiocyanate and polarographic methods to be 0.01 mg/kg dry weight, for atomic absorption 1 mg/kg and for neutron activation 0.02 mg/kg. No data on the accuracy of the methods for the determination of molybdenum in animal tissues and body fluids are available.

4. Production and uses

4.1 Production

Molybdenum does not occur naturally in the native state, but is obtained from the ores molybdenite, wulfenite, ferrimolybdate and jordicite. The overwhelming majority comes from molybdenite, the largest deposit of which is at Climax, Colorado, USA. The production of molybdenum (in countries excluding the USSR and some other countries in the Eastern hemisphere) increased from about 30,000 tons in 1960 to about 60,000 tons in 1969 (Minerals Yearbook, 1969).

4.2 Uses

The primary use of molybdenum is as a steel alloy. As such it is utilised in the weapons industry, in aeronautical engineering, and in the automobile industry. Of the US consumption in 1969, 84% was in alloys (Minerals Yearbook, 1969). In the chemical industry molybdenum compounds are used as catalysts and as chemical reagents. There are also many pigments that contain molybdenum compounds. Since molybdenum is an essential element in plant and animal nutrition, its uses include its addition to soil, plants and water to achieve various enrichment or balance effects.

5. Environmental levels and exposures

5.1 Food and daily intake

Daily intake of molybdenum can be estimated to be between 100 and 500 µg (Schroeder, 1970; Smolyar, 1972; Tipton and Stewart, 1970; Wester, 1971). In areas where molybdenum ore is mined, considerable contamination may occur, which can cause high concentrations in drinking water and daily intakes of more than 1,000 µg. The variations in foodstuffs, especially plants, are greatly dependent on species and soil characteristics. Generally, high concentrations are found in leafy vegetables and legumes, whereas edible roots have a lower content. Animal products are generally low in molydenum.

5.2 Water, soil and ambient air

Molybdenum in the ocean has been found to be around 0.01 mg/l (Sugawara et al., 1962; Muzzarelli and Rocchetti, 1973). American rivers ranged from 5 to 30 mg/l (Turekian and Scott, 1967). Molybdenum in normal soil seems to vary between 0.1-10 mg/kg (Reddy, 1964). In mining areas and near molybdenum-emitting industries considerably higher values have been reported (Chappell, 1974). Molybdenum in sewage sludge was found to vary between 2 and 30 mg/kg dry weight (Berrow and Webber, 1972). In ambient air in urban areas, molybdenum ranged 0.01-0.03 µg/m^3 and at nonurban sites 0.0001-0.0032 µg/m^3 (Schroeder, 1970).

6. Metabolism

6.1 Absorption

6.1.1 Inhalation

Guinea pigs did not show any noticeable absorption after an inhalation exposure to 285 mg Mo/m^3 as molybdenum disulfide while hexavalent molybdenum compounds were absorbed to an appreciable extent, even though this was not possible to quantify (Fairhall et al., 1945).

There are no human data on absorption of molybdenum after inhalation.

6.1.2 Ingestion

The gastrointestinal absorption is high in animals as well as in humans.

Animal data are from single exposure studies only. Hexavalent molybdenum is readily absorbed from the gastrointestinal tract, 40-85% in guinea pigs, rats and goats (Fairhall et al., 1945; Neilands et al., 1948; van Campen and Mitchell, 1965; Anke et al., 1971).

Tipton et al. (1969) found an absorption of more than 50% in two subjects and an absorption of probably less than 50% in one subject who participated in a balance study for over 50 weeks. An absorption of about 50% was also found by Wester (1974a).

6.2 Distribution

Studies of the distribution of molybdenum in guinea pigs and rats after a single oral exposure to molybdenum trioxide show an immediate accumulation in kidney, liver and bones. The same distribution is also seen after prolonged exposure in rats, cows and goats. The highest values are found in the kidneys (Fairhall et al., 1945; Robinson et al., 1964; Huber et al., 1971; Anke et al., 1971). In mice, after a single intravenous injection, the highest concentrations were found in the kidneys, liver and pancreas 1-24 hours after exposure. A decrease with time took place in the kidneys and pancreas while the concentrations of molybdenum in liver remained constant during the observation period (Rosoff and Spencer, 1973).

6.3 Excretion

Limited animal data indicate a low retention and a more or less complete excretion of molybdenum, primarily via urine, during the first two weeks after single exposures in guinea pigs, rats, goats and swine (Fairhall et al., 1945; Neilands et al., 1948; Bell et al., 1964; Anke et al., 1971; Kselikova et al., 1974). Excretion via urine was shown to have a half-time of 20 hours in cows (Robinson et al., 1964). In that same species, the main excretion route was reported to be feces by Bell et al. (1964). An important excretion route in connection with the gastro-intestinal excretion is the bile (Caujolle, 1937). Small amounts are excreted via milk and hair, in goats about 2% and 0.2% respectively (Anke et al., 1971).

Excretion in man was studied by Rosoff and Spencer (1964) after a single intravenous injection of radioactive molybdenum. The cumulative ^{99}Mo excretion in 10 days was 24% in one subject and 29% in another, while the corresponding fecal excretion was 5.8 and less than 1% respectively.

The total excretion of molybdenum in man during "normal" steady state conditions is not known. Data from Tipton et al. (1969) tend to show that 25-50% of the ingested amount is excreted via urine.

6.4 Biological half-time

The biological half-time has not been specifically studied. Data referred to above concerning excretion as well as the rapid clearance from liver, kidney, spleen and bones in animal studies show that the biological half-time, at least for the major part of the absorbed molybdenum, must be on the order of hours to a maximum of about one day in laboratory animals (Fairhall et al., 1945; Neilands et al., 1948) and perhaps up to a couple of weeks in humans (Rosoff and Spencer, 1964).

The concentration of molybdenum in blood decreases rapidly after a single subcutaneous injection in rats. After 24 hours only about 1% of the maximum concentration remained. During the next 10 days concentrations in blood diminished with a half-time of about 7 days (Kselikova et al., 1974).

7. Normal levels in tissues and biological fluids

In normal adults, median values for liver, kidneys and adrenals (spectrographically) have been found to be 1 mg/kg, 0.3 mg/kg and 0.7 mg/kg wet weight, respectively (Tipton and Cook, 1963). Plantin (1973) determined molybdenum in liver and kidney cortex by neutron activation in 8 autopsy cases in Sweden, 51-63 years of age. The average concentrations were 0.88 and 0.2 mg/kg wet weight. Kibluda (1964) reported the molybdenum concentration in liver and kidney of 80 subjects aged 17-77 years in the USSR. Arithmetic mean values for liver (thiocyanate method) were 0.5-0.6 mg/kg and for kidneys about 0.2 mg/kg wet weight.

An increase of molybdenum with age up to age 10-20 seems to take place in liver (Tipton and Cook, 1963; Schroeder et al., 1970).

Estimations of blood levels in different individuals show a wide scatter, but most data support a normal value of a few μg/l whole blood (Butt et al., 1964; Morgan and Holmes, 1972).

Data on daily urinary excretion of molybdenum in "normal" human subjects have been given by Meltzer et al. (1962) and Wester (1974b). On the average, the excretion in the groups varied between 49 and 71 μg/day.

8. Effects and dose-response relationships

Molybdenum is an essential element. It is a constituent of three mammalian metalloflavoproteins, xanthine oxidase, aldehyde oxidase and sulfite oxidase. No deficiency states in human beings have been reported.

8.1 Local effects and dose-response relationships

8.1.1 Animals

Inhalation of molybdenum compounds in high concentrations may be irritating to the upper respiratory tract. A few reports on inhalation or intratracheal administration have been published. Pneumoconiosis-like effects in the lungs have been reported in rats and rabbits. In one study rabbits were given intratracheally a suspension of powdered molybdenum of 70-80 mg/kg. In 9 months diffuse pneumoconiosis with interstitial pneumonia was observed upon histological examination (Mogilevskaya, 1963; Daukaev, 1970).

8.1.2 Humans

Pneumoconiosis with X-ray findings and subjective symptoms has been reported in 3 out of 19 workers exposed to metallic molybdenum and molybdenum trioxide (Mogilevskaya, 1963). Exposure varied between 1-19 mg/m^3 for 4-7 years.

8.2 Systemic effects and dose-response relationships

8.2.1 Laboratory animals

Acute as well as prolonged exposure to excessive molybdenum may give rise to morphological changes in thu liver, kidneys and spleen of rats, guinea pigs and rabbits. Proteinuria has been reported as well as different functional disturbances of the liver. Molybdenum has a growth depressive action. Other symptoms after prolonged exposure are anemia, diarrhea, and deformities of joints and long bones as well as mandibular exotoses (Ferguson et al., 1943; Arrington and Davis, 1953; Halverson et al., 1960; Dasler and Milliser, 1961; Ostrom et al., 1961; Valli et al., 1969; Mills and Mitchell, 1971).

Mandibular exostoses, growth retardation and anemia were found in rats on a diet containing 400 mg/kg of molybdenum as sodium molybdate for 5 weeks (Ostrom et al., 1961). Van Reen (1959) reported reduced growth and mandibular exostoses in rats fed 50 mg Mo/kg diet (given as Na_2MoO_4) plus a low sulfate supply.

8.2.2 Livestock

Evidence of chronic molybdenum poisoning has been seen in cattle and is known as "teart disease". This effect occurs after exposure to a diet high in molybdenum and low in copper. Symptoms include anemia, gastrointestinal disturbances, bone disorders, growth retardation, and impaired reproduction.

The molybdenum levels in typical teart pastures range from 20-100 mg/kg on a dry basis, compared with normal levels of 3-5 mg/kg (Ferguson et al., 1938; Ferguson et al., 1943; Hogan et al., 1971).

The disease has been possible to reproduce experimentally in cattle (Ferguson et al., 1943; Britton and Goss, 1946; Cook et al., 1966; Huber et al., 1971).

8.2.3 Humans

Increased blood uric acid values were reported in 34 out of 37 workers in a copper-molybdenum plant who complained of arthralgia (Akopajan, 1964).

A high incidence of a gout-like disease was reported in an area of Armenia having 77 mg Mo/kg and 39 mg Cu/kg in the soil (Koval'skiy et al., 1961; Yarovaya, 1964; Koval'skiy and Yarovaya, 1966). Based on copper and molybdenum levels in different food products, the intake in the exposed area was calculated to 10-15 mg molybdenum and 5-10 mg copper versus 1-2 mg molybdenum and 10-15 mg copper in the control area. In this region of the USSR more than 50% of the diet is based upon locally grown products. A medical survey of 400 subjects from two villages in the molybdenum-rich area revealed a prevalence of symptoms similar to gout in 31% in one of the villages and 18% in the other. The authors claimed that similar symptoms normally occurred in 1-4% of the population of the USSR. The symptoms were characterized as arthralgia in the knee-joints, hands and feet. Joint deformities were also reported as well as increased values of molydenum and uric acid in blood and urine. There are difficulties in interpreting the data due to possibilities of bias in connection with the selection of groups to be examined, but the data fully motivate further studies, not only in the USSR but also in regions of other countries where the exposure to molybdenum via the diet is high.

From the theoretical standpoint, effects like those reported in Armenia might well appear. Molybdenum exposure could give rise to an increase in xanthine oxidase activity which in turn should give rise to an increase in uric acid formation (Yarovaya, 1964; Gusev, 1969).

In humans, molybdenum has been shown to influence copper metabolism (see Chapter on Copper).

8.3 Interaction with copper and sulfur

There is a complex relationship between molybdenum, copper and sulfate, and probably also some other sulfur compounds. Species differences exist, e.g. sheep are more susceptible to imbalances between these elements than pigs. Copper generally has a beneficial effect on the symptoms caused by excessive molybdenum but the action of sulfur compounds, especially sulfate, is not so clearly understood, both positive and negative effects having been reported (Ferguson et al., 1943; Neilands et al., 1948; Arrington and Davis, 1953; Dick, 1953; Mills et al., 1958; Davis et al., 1960; Halverson et al., 1960; Compère et al., 1965; Lukasev and Siskova, 1969; Marcilese et al., 1969). Reference is also made to the monograph by Underwood (1971).

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SILVER

Gunnar F. Nordberg and Bruce A. Fowler

1. Abstract

Silver compounds may be absorbed via inhalation, but there are no quantitative data on the extent to which this will take place. Silver salts will be absorbed up to 10% following ingestion. The highest concentrations of silver are usually found in the liver and spleen and to some extent in the muscle, skin, and brain. The biological half-time for silver is on the order of a few days for animals and up to about 50 days for human liver; it is possible that skin deposits also have a long half-time, but there are no quantitative data on this in humans. Excretion of silver from the body is primarily gastrointestinal.

Silver is a non-essential element. Water soluble silver compounds such as the nitrate have a local corrosive effect and may cause fatal poisoning if swallowed accidentally. Chronic exposure of humans leads to argyria, a clinical entity characterized by gray-blue pigmentation of the skin and other body viscera. Repeated exposure of animals to silver may produce anemia, cardiac enlargement, growth retardation, and degenerative changes in the liver.

A review of environmental aspects of silver has been published by Carson and Smith (1975).

2. Physical and chemical properties

Silver, Ag, atomic number 47; atomic weight 107.9; density 10.5; melting point 960.8°C; boiling point 2212°C; crystalline form white metal, cubic 0.54; oxidation state +1, +2. Pure silver has the highest thermal and electrical conductivity of all metals. The metal forms important alloys with copper and other metals. The compounds of silver to be taken up here include silver nitrate, silver lactate, silver picrate, silver acetate and the silver halides.

3. Methods and problems of analysis

There are spectrographic, colorimetric, and polarographic techniques for measurement of silver. The detection limit for spectrographic and dithizone colorimetric methods has been put at 0.01 mg/l for a 20 ml sample (A.P.H.A. Standard Methods for the Examination of Water and Waste Water, 1966; Rooney, 1975). The detection limit for polarographic techniques is $5 \cdot 10^{-6}$M Ag (Cave and Hume, 1952). Atomic absorption (detection limit 2 µg/l) and neutron activation (detection limit 2 ng) may also be used and are relatively accurate. A reference listing of detection limits and other comments on the analysis for silver are given by Carson and Smith (1975).

4. Production and uses

4.1 Production

The main ore from which silver is produced is argentite. Silver is recovered from this ore by cyanide extraction, zinc reduction, or electrolytic processes. The world production of silver has increased from 238,400 million fine ounces in 1964 to 291,400 million fine ounces in 1972. Canada, Peru, USSR, United States and Mexico are the largest producers of silver (Carson and Smith, 1975).

4.2 Uses

Silver is used in the production of coins, jewellery and tableware. This element is also utilised as a component of various alloys and solders with copper, cadmium, and lead. It is extensively used in photographic processing, in the manufacture of electrical apparatus and mirrors, in dentistry, and in the treatment of burns (Harvey, 1970; Hartford and Ziffren, 1972; Sheker et al., 1972). Silver salts, because of their germicidal properties, are also used as drinking water disinfectants and as prophylactic agents against gonorrheal infection in the newborn.

5. Environmental levels and exposures

5.1 Food, water and soil

A detailed mapping of various dietary sources of silver is not available. Ingestion of silver may occur from consumption of marine organisms containing low concentrations (see below) and from small amounts released from dental fillings (Leirskar, 1974) and eating utensils (Harvey, 1970). Tipton et al. (1966) found that two subjects ingested between 0.02-0.01 mg/day from food during a 30-day period. Wester (1971), by neutron activation analysis, found a daily intake from food of 1-16 µg.

Sea water has been reported to contain silver concentrations of 0.055-1.5 µg/l (Schutz and Turekian, 1965). Much higher concentrations (0.03 mg/l) have been reported in waste water effluents entering southern California coastal basins (Galloway, 1972; Young et al., 1973; Bruland et al., 1974). Silver has been accumulated in concentrations of 14-20 mg/kg in bottom sediments in these areas (Galloway, 1972; Bruland et al., 1974). Molluscs collected from coastal areas of the North Sea have been reported to contain silver concentrations of up to 2.0 mg/kg (Segar et al., 1971; Dutton, 1973). Drinking water, not treated with silver for disinfection purposes, usually contains extremely low concentrations of silver. A range of non-detectable to 5 µg/l was reported for 380 finished waters from USA (Carson and Smith, 1975). Treated water may contain 50 µg/l or even slightly higher concentrations (Just and Szniolis, 1936). The United States drinking water standard for silver of 50 µg/l is rarely exceeded. Silver is infrequently found in rivers of the United States and then in concentrations of only about 1 µg/l (Kroner and Kopp, 1965). Concentrations of 5-150 µg/l have been reported in sewage sludge (Berrow and Webber, 1972).

Soil concentrations of silver vary greatly by geological area (Wells and Elliott, 1971). Granite igneous rock in Nevada has been reported to contain up to 50 mg/kg silver.

Coal flyash has been reported to contain up to 15 mg/kg silver (Headlee and Hunter, 1953) and emission of silver from coal-fired power plants may lead to its accumulation in soil of adjacent areas.

5.2 Ambient air and cigarettes

Silver has been measured in air as a result of anthropogenic activity. Air concentrations of silver over southern California have been reported to be about 2 ng/m^3 (Bruland et al., 1974). The emission of silver iodide crystals during cloud seeding has been estimated to result in a silver concentration in air of about 0.1 ng/m^3 (Sargent, 1969; Standler and Vonnegut, 1972). Silver concentrations in rainwater as a result of this process were estimated to be between 0.04 pg/ml and 5 ng/ml.

Concentrations of silver in cigarettes are low. Because of its high boiling point, most of the silver in cigarettes is probably not inhaled.

6. Metabolism

6.1 Absorption

6.1.1 Inhalation

The deposition fraction of 0.5 micron spherical silver particles in the lung of dogs has been found to be about 17% (Phalen and Morrow, 1973). Newton and Holmes (1966) studied the long-term retention in a human who accidentally inhaled radioactive silver (chemical form not known). Their data indicated that the liver uptake was maximal less than two weeks after inhalation, suggesting absorption of alveolarly deposited silver compounds, although it cannot be excluded that a part of the silver compounds was cleared to the gastrointestinal tract and absorbed that way.

6.1.2 Ingestion

The intestinal absorption of silver by mice, rats, monkeys, and dogs has been recorded at about 10% or less following ingestion of radioactive silver (Furchner et al., 1968). No precise data are currently available for humans.

6.2 Distribution

Dogs exposed to silver by inhalation accumulated most of the administered dose in the liver, with lower concentrations in the lung, brain, and muscle (Phalen and Morrow, 1973). Studies on rodents have also indicated a high initial concentration of silver in the liver which decreases greatly within 10 days, while silver concentrations in the spleen and brain are retained for longer time periods (Gammill et al., 1950; Furchner et al., 1968). In a human being more than 50% of the body burden of silver was found in the liver 16 days and later after exposure (Newton and Holmes, 1966).

6.3 Excretion

Mice, rats, monkeys, and dogs given radioactive silver salts by oral, intravenous, or intraperitoneal routes were found to excrete over 90% of the absorbed dose via the feces (Furchner et al., 1968). The fecal elimination is mainly explained by biliary excretion (Scott and Hamilton, 1948). Fecal elimination has also been found to be the primary excretory pathway following inhalation exposure to silver in dogs (Phalen and Morrow, 1973) and in humans (Newton and Holmes, 1966).

6.4 Biological half-time

After rabbits had inhaled 4 micron monodisperse silver-coated teflon particles, Camner et al. (1974) found an average of 30% of the deposited part to be cleared from the lung in one day and another 30% during the rest of the first week of the exposure. After inhalation exposure, dogs cleared 59% of an administered dose of radioactive silver from the lungs in 1.7 days (Phalen and Morrow, 1973). The liver had a somewhat slower clearance of 9 days. A biological half-time of about 1 day was found by whole-body scintillation counting in mice, rats, monkeys, and dogs after oral ingestion, mainly due to fecal elimination of unabsorbed silver (Furchner et al., 1966). Longer biological half-times were observed for all these species after intravenous injection of silver, with monkeys and dogs having biological half-times of 1.8 and 2.4 days respectively. Silver injected into rats as radioactive silver nitrate had a biological half-time of 2.2 days (Habighorst and Buchwald, 1971). The biological half-time of silver in the lungs of a human exposed to silver has been estimated to be 1 day while that in the liver was 52 days (Newton and Holmes, 1966). In a carcinoid patient Polachek et al. (1960) estimated a biological half-time of 48 days in the liver by external counting after i.v. injection of radioactive silver. Upon postmortem examination 195 days after injection the highest concentration of radioactive silver was found in the liver and the second highest in skin, indicating a relatively long biological half-time for skin as well.

7. Normal levels in tissues and biological fluids

The concentrations of silver in kidneys, liver, and spleen of "normal people" have been reported to be about 0.4, 0.7, and 2.7 mg/kg respectively on a dry weight basis (Indraprasit et al., 1974). Normal concentration in skin was reported as 0.035±0.015 mg/kg dry weight by Schröpl et al. (1968). Hamilton et al. (1972) reported 0.006±0.002 mg/kg wet weight in liver, 0.001±0.002 in kidney and 0.002±0.0001 in lung.

Tipton et al. (1966) found between 0.006-0.015 mg/day in urine and between 0.02-0.11 mg in feces. Wester (1971) (neutron activation) found 0.9-1 μg/day in urine and 0.9-97 μg/day in feces. In urine Boström and Wester (1968) found 1 μg/24 h in normal persons and 0.7-7.5 μg/24 h in patients with untreated hyperthyroidism.

8. Effects and dose-response relationships

8.1 Local effects and dose-response relationships

Silver salts are pronouncedly caustic and have been used widely in the treatment of warts. Silver salts are used for the treatment of burns and have a strong antiseptic effect. Dressings soaked with 0.5% $AgNO_3$ have been extensively used without any evident local or systemic silver toxicity (Hartford, 1972).

Repeated occupational handling of silver objects, especially if repeated minor injury is involved, may give rise to so-called local argyria, which is blueish-gray discoloration of the skin at the exposed site. This condition is considered harmless apart from aesthetic considerations (cf. Holzegel, 1970, and others).

8.2 Systemic effects and dose-response relationships

8.2.1 Animals

The primary toxic effects of silver seem to be exerted on the cardiovascular, hepatic, and hematopoietic systems. Cardiac enlargement and ventricular hypertrophy have been reported in turkeys following dietary exposure to 900 mg/kg silver nitrate for 18 weeks (Peterson et al., 1973; Jensen et al., 1974). A 28.6% mortality figure was recorded for treated animals during the course of the study. Decreased aortic elastin content has also been observed (Olcott, 1948; Peterson et al., 1974; Jensen et al., 1974). Centrilobular hepatic necrosis and ultrastructural alteration of mitochondria and lysosomes have been described in livers of vitamin E deficient rats exposed to silver (Grasso et al., 1970).

Anemia of a microcytic, hyperchromic type is a common finding among animals chronically exposed to dietary levels of several hundred mg/kg of silver compounds (Shouse and Whipple, 1931; Peterson et al., 1973; Jensen et al., 1974).

8.2.2 Humans

Acute effects. 50 mg or more of collargol (Ag-salt) has been reported to be lethal after intravenous injection for therapeutic purposes. Autopsy findings in such cases have included pulmonary edema, hemorrhage and necrosis of bone marrow, liver and kidney (Patein and Robin, 1909; Hill and Pillsbury, 1959). Intrauterine administration of approximately 25 g of silver nitrate has been reported to be rapidly fatal to a human (Reinhart et al., 1971).

Chronic effects. Repeated exposure to silver salts or colloidal silver by inhalation or ingestion brings about effects classically described as generalized argyria. This clinical entity is characterised by a gray-blue discoloration of skin, most pronounced in areas exposed to light (Holzegel, 1970; Breton et al., 1971; Kügler et al., 1972; Rich et al., 1972; Buckley and Terhaar, 1973; Lehnert, 1973; Hönigsman et al., 1973; Hanna et al., 1974). Deposition of silver compounds causing discoloration and sometimes also functional impairment and/or clinical symptoms may also occur in other organs.

Deposition of silver compounds in the cornea and the anterior capsule of the lens as may be detected by slit-lamp examination (Larsen, 1927; Velhagen, 1953; Koelsch, 1956) causes some impairment of vision in exceptional cases.

Argyrosis of the respiratory tract, liver, kidney and gastrointestinal tract has been reported and may be associated with certain clinical symptoms such as chronic bronchitis (Montaudon, 1959) and abdominal discomfort (Frankun and Langhof, 1964). However, since these case reports have not been properly evaluated in relation to reference groups, it is impossible to say whether there is a true causal relationship between exposure to silver and these symptoms.

The exposure conditions giving rise to argyria have not been well defined. Evaluation of the older literature (Hill and Pillsbury, 1959) indicated that a total dose of 1-8 g Ag would be required to induce the condition in a long-term inhalation exposure situation.

The dosage required to induce argyrosis by ingestion seems to be somewhat higher, i.e. between 1-30 g of soluble silver salts (Lehnert, 1973). Silver in metallic form is harmless. Blond people are considered more susceptible than others.

The tissue concentrations leading to argyrosis have not been extensively studied; Schröpl et al. (1968) found 63±8 mg/kg dry weight in skin samples from persons with argyrosis. Ultrastructural examination of skin biopsies from patients with argyrosis has demonstrated silver deposition in the basal lamina of the various skin layers (Hönigsman et al., 1973) as well as in the sweat glands (Lehnert, 1973).

8.3 Interactions with selenium, copper and vitamin E

Dietary administration of silver acetate has been found to antagonize selenium toxicity (Diplock et al., 1967). Conversely, addition of selenium, copper and vitamin E to the diet in varying concentrations has been reported to decrease the toxicity of silver (900 mg/kg in diet as silver acetate) to turkey poults (Jensen et al., 1974). Addition of selenium to the diets of rats exposed to silver in drinking water prevented growth retardation but increased hepatic and renal concentrations of silver (Wagner et al., 1975).

9. Treatment

There is no recognised effective treatment for argyrosis. The condition seems to be relatively stationary when exposure to silver is discontinued. Chelation therapy is considered ineffective (Lehnert, 1973).

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TELLURIUM

V.B. Vouk

1. Abstract

There is no quantitative information on the absorption of inhaled tellurium compounds. About 10-20% of ingested tellurite ion is absorbed and first distributed in blood and soft tissue, mainly kidney and liver. Accumulation of tellurium in the bone is slow but 90% of the body burden in man is found there. Tellurium is also deposited in the neural and glial cells, and penetrates placenta. Ingested tellurium compounds are largely eliminated in feces; the absorbed fraction is excreted mainly in urine but also in feces. Very small amounts are excreted by exhalation as methyl telluride. The estimated half-times for blood, liver and kidney of the rat range from 9 - 23 days; for bone it is very long, a rough estimate being two years or more.

There is no evidence that tellurium is essential either to man or animals.

Organs most affected in acute and subacute poisoning of animals are the liver, kidney, nervous system, lungs and the gastrointestinal tract. The affects of tellurium on the nervous syetem of rats include paralysis of hind legs, alteration of conditioned reflexes and reduced learning ability. There is no evidence of carcinogenicity but hydrocephalus was found in rats born to mothers on a diet containing high levels of elemental tellurium.

A garlic odor of the breath, sweat and urine, dryness of the mouth, suppression of sweat, and metallic taste in the mouth are the main symptoms and signs of occupational exposure to tellurium compounds. A few cases of non-occupational fatal poisoning by sodium tellurite have been reported. There is no specific antidote for tellurium poisoning.

Inhalation is the main route of exposure under occupational conditions; for the general population the main source of tellurium is food.

Reviews of tellurium toxicology were published by Cerwenka and Cooper (1961), Sandrackaja (1963), Browning (1969) and Israel'son (1973).

2. Physical and chemical properties

Tellurium, Te, periodic system group VIb; atomic weight 127.6; atomic number 52; density 6.2 (20°C); melting point 449.5°C; boiling point 989.8°C; in elemental state it is a coarsely crystalline silver-white solid with metallic lustre; amorphous tellurium is a fine black powder. Its chemistry is similar to that of selenium, but tellurium has more pronounced metallic properties. Tellurium forms compounds in oxidation states -2, +2, +4 and +6. Of toxicological interest are elemental tellurium, hydrogen telluride and tellurium hexafluoride, both colorless gases; tellurium dioxide; tellurous and telluric acids; and sodium and potassium tellurites and tellurates which are soluble in water. There are many organometallic and complex compounds of tellurium.

3. Methods and problems of analysis

The most promising analytical techniques for tellurium in environmental and biological samples are atomic absorption spectrometry and neutron activation but they require further development. The limit of detection of AAS in air-hydrogen flame at 214.3 nm is about 0.1 mg/l (Chakrabarti, 1967; Severne and Brooks, 1972). Estimated limit of detection for slow neutron activation (n, γ-reactions) is of the order of 0.1-0.2 μg (Parsons, 1976). The available information is inadequate to assess the precision and accuracy of these methods. Kinser (1966) reported a relative standard deviation of about ±5% for AAS with wet ashing of tissue samples. The inaccurate pretreatment of biological samples can result in considerable analytical errors (Nason and Schroeder, 1967). The separation of tellurium from selenium and other elements can be achieved by several procedures, including chromatography (Fishbein, 1973).

4. Production and uses

4.1 Production

There are no ore deposits which could be mined for tellurium only and its recovery is linked with the production of copper, lead, and other metals. The estimated world production of tellurium in 1971 was of the order of 200 tons (Kudryavtsev, 1974). Electrolytic copper refining is the source for 80% of the world's supply of tellurium. The remainder is recovered from slimes and slags of lead refining, and from pyrite and pyrrhotite burned in pulp and paper mills and sulfuric acid plants.

4.2 Uses

The estimated tellurium consumption in metallurgy is 79%; in chemical, rubber, plastics and glass industries 18%; and for electrical and electronic uses 3%. In ferrous and non-ferrous metallurgy it is used to improve the technological properties of steels, cast iron, and copper and lead base alloys. Powdered tellurium is a secondary vulcanizing agent; in combination with some other organic compounds tellurium diethyldithiocarbamate is an excellent accelerator for butyl rubber. Tellurium is also used in catalysts, metal finishing, explosives, antioxidants, infra-red transmitting glasses, and in thermoelectric and other electronic devices (Kudryavtsev, 1974). Some tellurium compounds found therapeutic applications (Browning, 1969).

5. Environmental levels and exposures

5.1 General environment

5.1.1 Food

Schroeder et al. (1967) have found the following mean values in food samples (in mg/kg): - meats 4.2; dairy products 4.8; cereals 2.8; fats and oils 1.8; vegetables and fruits 1.1; hospital diets 0.44. Most of these values are probably too high (about 80%) and should be considered as a rough approximation only (Nason and Schroeder, 1967). After revising the results of Schroeder et al. (1967), Nason and Schroeder (1967) estimated the daily intake at about 100 µg.

5.1.2 Water and ambient air

Tellurium concentrations in water are probably very low as no Te could be detected in 20 samples of tap water from one location in the USA (Schroeder et al., 1967). No spectrographically detectable quantities of tellurium were found in the principal USA rivers (Durum, 1960).

Tellurium in ambient air originates from industrial emissions and coal combustion. An estimate has been made that coal combustion in the USA releases about 40 tons of Te in fly ash (Davidson and Lakin, 1972). Seljankina and Alekseeva (1971) found about 2 µg Te/m^3 at 2 km from an electrolytic copper refining plant.

5.2 Working environment

Since the production and use of tellurium is linked with other metallurgical and industrial processes, there is a possibility of multiple occupational exposures which may involve lead, zinc, arsenic, selenium, cadmium and thallium. There is little information on the levels of exposure and on the chemical form of tellurium in the working environment. In addition to elemental tellurium, occupational exposures may include tellurium dioxide and hydrogen telluride (Izrael'son, 1973). Steinberg et al. (1942) reported air levels of tellurium in an iron foundry ranging from 0.01 to 0.1 mg/m^3 with 70% of the results falling between 0.01 and 0.05 mg/m^3.

6. Metabolism

Data on tellurium metabolism have been summarised by ICRP (1968). There is practically no information on the metabolism of tellurates.

6.1 Absorption

6.1.1 Inhalation

There is no quantitative information on the respiratory absorption of tellurium compounds.

6.1.2 Ingestion

The absorption of ingested elemental tellurium and of tellurium dioxides cannot be quantified on the basis of available information (De Meio, 1946; De Meio and Jetter, 1948).

Gastrointestinal absorption of tellurites is completed within two hours and takes place, in rat, mainly in the duodenum and jejunum (Slouka and Hradil, 1970). Absorption estimates vary from 10-15% (Hollins, 1909) to 25% (Slouka and Hradil, 1970). In swine as in sheep, sodium tellurite is absorbed from the colon but not from the small intestine (Wright and Bell, 1966).

6.2 Distribution

The method of administration (i.v. and i.p. injection, oral) does not significantly change the pattern of soft tissue distribution of tellurium given as sodium tellurite or tellurous acid in HCl solution (De Meio and Henriques, 1946; Moskalev, 1960; Hollins, 1969; Slouka, 1970; Slouka and Hradil, 1970). A short term equilibrium is reached within 1-2 hours; the organs of highest concentration include the kidney, liver, lungs, thyroid, spleen and the blood. The uptake by skeletal muscles is much slower, and in the long-term tellurium seems to accumulate in the bone (Hollins, 1969; Slouka, 1970).

About 90% of blood tellurium in the rat is contained in the erythrocytes, probably bound to hemoglobin (Sandratskaja and Krasovskij, 1963; Hollins, 1969; Slouka, 1970; Agnew and Cheng, 1971). The same applies to swine but not sheep where only a small fraction of tellurium was found in washed blood cells following oral and intravenous administration of sodium tellurite (Wright and Bell, 1966). Tellurium deposited in various tissues of the rat is bound to soluble proteins (58-96%) (Agnew and Cheng, 1971).

Agnew et al. (1968) demonstrated that tellurium readily crossed the blood brain barrier of the rat. In rats maintained on a diet with high concentrations of elemental tellurium (3000 mg/kg), fine needles of tellurium were found in the lysosomes of the brain neurons (Cravioto et al., 1968). A similar observation was made by Mizuno (1969) on rabbits which received an i.m. injection of elemental tellurium suspended in olive oil.

Transplacental uptake of tellurium was shown by Agnew (1972) in rats receiving i.p. injections of radioactive tellurous acid in 0.9 M HCl.

6.3 Excretion

Injected tellurium (i.v. and i.p. as sodium tellurite) is excreted by the rat mainly with urine (14-27% within 24 hours, 33% within one week). Fecal excretion amounts to about 6% in 24 hours and 14% in one week. Tellurium is transferred to the intestine by biliary excretion (Hollins, 1969; Slouka, 1970). About 11-16% of i.v. injected Te (as sodium tellurite) was excreted by female dogs within one hour, and 23% within 6 days (De Meio and Henriques, 1947).

About 60-80% of ingested sodium tellurite and tellurium dioxide was rapidly eliminated by rats and swine in feces (De Meio and Henriques, 1947; Sandrackaja and Krasovskij, 1963; Wright and Bell, 1966; Slouka and Hradil, 1970; Chertok and Lake, 1971). Urinary excretion is highest within 7-24 hours; it amounts to 3-9% in 6-11 days in rats and female dogs, and to 17-20% in 1-3 days in swine (De Meio and Henriques, 1947; Sandrackaja and Krasovskij, 1962; Wright and Bell, 1966; Chertok and Lake, 1971).

During the first 4 days after a single feeding of ^{132}Te (chemical form not specified), 0.3-0.5% was excreted in sheep milk. This is very close to the value reported for dairy cows (0.5% in 6 days) (Casey et al., 1963).

A very small amount of absorbed tellurium is exhaled (about 0.1%) presumably as dimethyltelluride producing a garlic-like odor noted in animals and man after exposure to elemental tellurium and tellurium (IV) compounds (Steinberg et al., 1942; De Meio, 1946; De Meio and Henriques, 1947; Amdur, 1958; Popova et al., 1965; Hollins, 1969). Schroeder et al. (1967) consider that tellurates are not methylated in the organism.

6.4 Biological half-time

The whole body retention of tellurium in rats after i.p. or i.v. injection of tellurous acid in HCl or sodium tellurite can be described by a sum of two exponential functions with biological half-times of about 19 hours (42-49% of dose) and 13-15 days (51-58%) (Hollins, 1969; Slouka, 1970). After gavage of the same compounds a third exponential term (half-time of 3-7 hours) has to be added to account for the rapid elimination of the non-absorbed fraction (70-86%) (Hollins, 1969; Slouka and Hradil, 1970). The whole body retention model for man (ICRP, 1968) assumes a biological half-time of about 3 weeks.

Hollins (1969) estimated the biological half-times for the major sites of retention of tellurium as 9.2 days (blood), 10.2 days (liver), 17.7 days (muscle) and 23 days (kidney). His results for femur suggest that bone practically does not release deposited tellurium; a very crude estimate of the half-time is 600 days with a standard error of 5000 days.

7. Normal levels in tissues and biological fluids

There is no reliable information on the "normal" values in man. Data reported by Schroeder et al. (1967) and revised by Nason and Schroeder (1967) are a very crude approximation because of the analytical inconsistencies admitted by the authors themselves. It is nevertheless of interest to note that the skeleton was estimated to contain more than 90% of the total body burden (about 500 mg, based on neutron activation data).

8. Effects and dose-response relationships

There is no evidence that tellurium is essential either for man or animals.

8.1 Local effects and dose-response relationships

8.1.1 Animals

Inhalation of elemental tellurium and tellurium dioxide aerosols (10, 50 and 100 mg/m^3, 2 hours daily, 13-15 weeks) produced in rats catarrhal desquamatory bronchitis and lobar pneumonia (Sandrackaja, 1962a; Izrael'son, 1973). Inhalation of tellurium hexafluoride (50 mg/m^3, 1 hour) resulted in pulmonary edema in rabbits, guinea pigs, rats and mice (Kimmerle, 1960).

Long-term ingestion of sodium tellurite and tellurate (1-50 mg/kg body weight, 3-7 months) was accompanied by dark inclusions and degenerative changes in the small intestines of rats and rabbits (El'nicnik and Lencenko, 1969) but pekin ducks kept on a diet of tellurium tetrachloride (50-1000 mg Te/kg, 2-4 weeks) showed only a gray-black discoloration of the intestines (Carlton and Kelly, 1967).

Tellurium dioxide caused inflammatory processes when in contact with rat's digits (De Meio and Jetter, 1948).

8.1.2 Humans

Exposures to tellurium vapor and hydrogen telluride have been reported to cause irritation of the respiratory tract (Popova et al., 1965; Izrael'son, 1973).

The evidence of local effects on the skin following occupational exposure to fumes and dust containing tellurium dioxide is not conclusive (Shie and Deeds, 1920).

8.2 Systemic effects and dose-response relationships

8.2.1 Animals

The signs of systemic toxicity of tellurium and its compounds observed in acute and subacute studies include listlessness, decreased locomotor activity, somnolence, anorexia, loss of weight, and gastrointestinal disturbances; changes in fur coat, and occasionally, epilation and paralysis of hind legs were noticed in rats (De Meio, 1946; De Meio and Jetter, 1948; Amdur, 1958; Sandrackaja, 1962a). Life-time exposure of rats to sodium tellurite and of mice to sodium tellurite and tellurate (2 mg Te/l drinking water) had no effect on growth and survival rate of males, but tellurite reduced the life-span of female mice (Schroeder and Mitchener, 1971 and 1972).

8.2.1.1 Liver

Pathomorphological changes in the liver reported as resulting from exposure to tellurium compounds range from simple cellular swelling to hydropic and fatty degeneration and cell necrosis. Such observations were made by De Meio and Jetter (1948) (rats, tellurium dioxide ingestion, 375-1500 mg/kg diet, 24-128 days), Sandrackaja (1962b) (tellurium dioxide, inhalation exposure, 50 mg/m^3, 2 hours daily, 13-15 weeks), Lencenko (1966) and El'nicnik and Lencenko (1969) (rats and rabbits, sodium tellurite, gavage of 5 and 10 mg/kg body weight for 3 months, and of 0.5 mg/kg for 7 months) and Carlton and Kelly (1967) (pekin ducks, 50-1000 mg/kg diet as tellurium tetrachloride, 2-4 weeks).

Impairment of glycogen function, detoxifying functions and of protein metabolism as indicated by dose-related reduction of galactose tolerance, hippuric acid excretion, decrease of albumin/globulin ratio in serum, urinary bilirubin excretion, inhibition of cholinesterase, etc. were observed by Sandrackaja (1962b) (rats, inhalation exposure to tellurium dioxide), Lencenko (1966) and Lencenko and Piotho (1969) (subacute and chronic studies in rats and rabbits, oral administration of sodium tellurite, 0.5-10 mg Te/kg body weight).

8.2.1.2 Kidney

Inhalation exposure of rats to tellurium dioxide (condensation aerosol, 10 and 50 mg/m^3, 2 hours daily, 13-15 weeks) caused focal vacuolisation of cells and hemorrhage in the glomeruli, accompanied by albuminuria and hematuria (Sandrackaja, 1962a, 1962b). Ingestion of tellurium dioxide (375-1500 mg Te/kg diet, 24-128 days) induced changes ranging from cellular swelling to frank necrosis, accompanied in some rats by oliguria and anuria, indicating severe lesions in the proximal tubular epithelium (De Meio and Jetter, 1948). Kidneys were soft, swollen, grossly hemorrhagic and distinctly necrotic in guinea pigs after a single i.m. injection of 75 mg tellurium dioxide; these effects were probably enhanced by BAL administered to some animals together with TeO_2. No kidney lesions were reported in subacute and chronic studies with sodium tellurite in rats and rabbits (El'nicnik and Lencenko, 1969).

8.2.1.3 Blood

Sandrackaja (1962a, 1962b) reported normochromic, possibly hemolytic, anemia in rats exposed to tellurium dioxide and elemental tellurium aerosol (50-100 mg/m^3, 2 hours daily, 13-15 weeks), indicated by dose-related reductions in hemoglobin and erythrocytes, and hematuria. No significant changes in the peripheral blood were noted by De Meio and Jetter (1948) in feeding experiments on rats (tellurium dioxide, 375-1500 mg/kg diet, 24-128 days), and by Lencenko (1966) in subacute and chronic experiments in rats and rabbits (0.0005-1 mg Te/ kg body weight, 3-7 months).

8.2.1.4 Heart

Carlton and Kelly (1967) observed myocardial hemorrhage, hydropericardium and areas of necrosis confined to myocardium in pekin ducks maintained on a diet containing tellurium tetrachloride (50-1000 mg Te/kg diet, 2-4 weeks).

8.2.1.5 Nervous system

Weakness and/or paralysis of hind legs in rats observed by several authors under different experimental conditions

(De Meio and Jetter, 1948; Amdur, 1958; Sandrackaja, 1962a, 1962b; for definitions of exposure see previous sections) was recently confirmed by Lampert et al. (1970) and Lampert and Garret (1971) who administered 1-1.25% of elemental tellurium to young rats for 1-8 days. These authors consider that the paralysis is caused by demyelinisation of sciatic nerves resulting from degeneration of Schwann's cells.

Morphological changes in the pyramidal cells of the brain cortex were found in rats ingesting sodium tellurite and tellurate for 3-7 months (Lencenko, 1966; El'nicnik and Lencenko, 1969). Focal as well as more extensive areas of necrosis were observed in the brain of pekin ducks fed tellurium tetrachloride for 2-4 weeks (100, 500 and 1000 mg Te/kg diet; Carlton and Kelly, 1967).

These morphological changes are either preceded or associated with functional and biochemical changes, including impaired conditioned reflexes (Lencenko, 1966), increased chronaxie (Sandrackaja, 1962a, 1962b) and inhibition of cholinesterase and free thiol groups in the gray matter of the brain (Lencenko and Flotho, 1969). A severe impairment of the learning ability resulted from exposure of weanling rats for 6 months to elemental tellurium (3000 mg/kg diet).

8.2.1.6 Miscellaneous biochemical effects

Sodium tellurite given orally to rats for 7 months at daily doses of 0.005 mg Te/kg or more reduced the activity of catalase and free thiol groups in the blood (Lencenko, 1966). Inhibition of catalase in the erythrocytes was noted also by Sandrackaja (1962a, 1962b) in rats exposed to tellurium and tellurium dioxide aerosols. Tellurite ion (1 mM) added *in vitro* to the mitochondria of rat's kidney and liver selectively inhibited the oxidation of NAD dependent substrates (Siliprandi et al., 1971). Administration of sodium tellurite (150 µg Te/kg body weight/day) for 11-30 months to weanling rats in diet and drinking water increased serum cholesterol in male but not in female animals (Schroeder, 1968).

8.2.2 Humans

8.2.2.1 Occupational exposures

Shie and Deeds (1920) examined 13 subjects working around blast furnaces where the slime of an electrolytic lead refinery was treated. No data are available on the level of exposure, but the authors consider that tellurium could have been present in the form of hydrogen telluride as well as tellurium dioxide dust. Seven out of 13 examined workers showed evidence of tellurium absorption by garlic odor of the breath, sweat and urine, dryness of the mouth and metallic taste. Five had a considerable inhibition of the sweat function, and 3 of them had a dry and itchy skin, anorexia, nausea, some vomiting, depression and somnolence which were regarded by the authors as signs and symptoms of mild tellurium poisoning. Steinberg et al. (1942) found garlic odor of breath in 84 and of sweat in 30 out of 98 workers exposed to tellurium-containing fumes in an iron foundry (0.01-0.1 mg Te/m^3, 22 months). Tellurium was found in urine of all exposed workers (0.01-0.06 mg/l) but not in any of the control group. The workers complained of garlic odor of breath and sweat, dryness and metallic taste in the mouth, somnolence, loss of appetite and occasional nausea. Similar signs and symptoms were found by Amdur (1947) in 3 laboratory workers accidentally exposed to tellurium-containing fumes for not more than 30 minutes. Tellurium was present in urine (0.008-0.016 mg/l).

Popova et al. (1965) described two cases of non-fatal occupational poisoning by tellurium vapor, but no information was given on the possible level of exposure. Signs and symptoms included general weakness, cough, shivering, amnesia, pallor of the skin, and black-green discoloration of mucosa of the tongue and nasopharynx. Temperature and pulse rate were increased, and moderate leukopenia, neutrophilia and leucocytosis were present. The breath smelled of garlic. The ECG showed transient diffuse changes in the electrical activity of the myocardium.

8.2.2.2 Accidental non-occupational exposure

Keal et al. (1946) described 3 cases of accidental tellurium poisoning where sodium tellurite solutions were given instead of potassium iodide during retrograde pyelography. In two cases the dose was about 2 g (≈30 mg/kg). Two patients died after about 6 hours; death was preceded by vomiting, renal pain, stupor, loss of consciousness, irregular breathing and cyanosis. Autopsy revealed deposition of black tellurium in the mucosa of the bladder and of the ureter, and congestion of lungs, liver, spleen and kidneys and fatty change of the liver. All tissues emitted a strong garlic odor.

8.3 Carcinogenicity, teratogenicity and mutagenicity

Schroeder and Mitchener (1971, 1972) exposed rats to sodium tellurite and mice to sodium tellurite and sodium tellurate for life (2 mg Te/l drinking water). There was no evidence that such exposure changed either the tumor incidence or the time-to-occurrence of tumors.

Tellurium was found to induce hydrocephalus in newborn rats of mothers fed high concentrations of elemental tellurium (Garro and Pentschew, 1964; Agnew et al., 1968; Duckett, 1971, 1972). Sixty to 100% of litters had hydrocephalus with an incidence of 25-100%. The sensitive period of teratogenic vulnerability was between day 9 and 15 of gestation (Duckett et al., 1972; Agnew and Curry, 1972). It seems that tellurium acts directly on the embryo (Agnew, 1972).

There are no animal studies on the mutagenicity of tellurium compounds. A significant increase of chromosome breakage incidence was, however, observed in human leukocytes treated *in vitro* with sodium tellurite ($1.2\cdot10^{-8}$M) and ammonium tellurite ($2.4\cdot10^{-7}$M) (Patton and Allison, 1972).

9. Diagnosis and treatment

Garlic odor of the breath and urine, and the presence of tellurium in urine are sensitive indicators of tellurium absorption. Garlic odor of the breath was noticeable in 5 volunteers who ingested 3 mg tellurium (compound not specified) in 10 ml water each day for 8 days (Lencenko, 1966), corresponding to a daily intake of about 40 µg/kg.

There is no specific antidote for poisoning by tellurium compounds. The use of BAL or ascorbic acid is not recommended (Amdur, 1958).

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THALLIUM

George Kazantzis

1. Abstract

Following rapid, almost total, absorption from the gastrointestinal tract, soluble thallium salts are widely distributed in the body, the highest concentrations being attained in the kidney. Excretion occurs in both urine and feces, the disappearance of thallium from the tissues following first order kinetics. The biological half-time of ^{204}Tl in the rat has been calculated at three to four days. In man, thallium may be found in urine and feces for several weeks following absorption. Excretion also occurs via hair, which in unexposed subjects has been shown to contain the highest concentration of thallium in any tissue. In the rat, 21 days after dosing, up to 60% of the remaining body burden was found in the hair. There are similarities in the ionic transport of thallium and potassium through cell membranes, but once intracellular, thallium is less rapidly released than potassium.

Thallium salts have caused acute and often fatal poisoning as a result of accidental, criminal or suicidal ingestion. Fatalities have also occurred following the therapeutic administration of thallium. Following industrial exposure a number of cases of chronic poisoning have been observed. Gastroenteritis, peripheral neuropathy and collapse are the principal features in acute poisoning, but with longer survival, alopecia becomes characteristic. In chronic poisoning the main features are vague ill health, paresthesias and alopecia. The widespread use of thallium as a pesticide has been responsible for the death of domestic and wild animals and their natural predators.

2. Physical and chemical properties

Thallium, Tl, atomic weight 204.4; atomic number 81;

density 11.9; melting point 303.5°C; boiling point 1457°C; crystalline form blue-white metal, tetragonal; oxidation state, 1, 3. Compounds to be taken up in this treatise are thallous sulfate, thallous nitrate, and thallium acetate. Other common compounds are thallium (I) oxide, thallium (III) oxide, thallous carbonate and thallous sulfide.

Thallium shares group IIIb of the periodic table with indium, gallium, aluminum and boron. It is softer than lead. Thallium metal forms a brownish-black oxide upon exposure to air. Thallium is highly reactive, readily soluble in acids and forms monovalent thallous and trivalent thallic salts, the latter of which are less stable.

3. Methods and problems of analysis

Thallium can be readily identified spectrographically, as described by Truhaut (1959) and Downs et al. (1960). Thallium in body fluids or tissues can be precisely estimated by atomic absorption spectrophotometry following conversion to thallic bromide (Savory et al., 1968). The limit of detection of the method is 3.5 mg Tl/50 l sample of urine and 3.5 µg Tl/5 ml sample of serum. A coefficient of variation of 6.9% has been given for duplicate analyses of thallium in urine specimens containing 100 to 300 µg/l. The method is free from appreciable interference by other elements. Thallium has been estimated in urine using a carbon rod atomizer and atomic absorption spectrophotometry (Kubasik et al., 1973). Thallium in small samples on the order of 0.1 to 2 g of liver or kidney has been estimated by pulse polarography (Reinhardt and Zink, 1973). Care is required with the purity of the reagents to obviate interference from lead. The detection limit in such samples is 0.1 mg/kg, which level may be indicative of poisoning. Thallium poisoning has been detected from single hair and toenail samples by means of neutron activation analysis (Henke and Fitzek, 1971). The detection limit of the method has been given as 10^{-4} mg/kg. Two simple colorimetric methods for the determination of thallium in urine are the Rhodamine B method (Duvivier et al., 1964; Bank et al., 1972) and the methyl violet method (Rieders, 1971), the latter having a detection limit of 0.15 µg thallium.

4. Production and uses

4.1 Production

Thallium is found in Texas and Brazil, in the minerals lorandite and crooksite. However, it is usually recovered from flue-dust residues from zinc and lead smelters and as a by-product of cadmium production. Thallium, which is present as a sulfate, is separated by electrolysis. It is also obtained from the residues in the production of sulfuric acid by the lead chamber process. Total production is unlikely to exceed a few thousand tons per annum.

4.2 Uses

Thallium has been used on a large scale as a pesticide, mainly as a rodenticide, but has been replaced in some countries by safer compounds. However, in some areas, following the development of warfarin resistance in rats, the use of thallium has recently increased. Thallium compounds have uses in infra-red and other optical systems on account of their high refractive index. They are also used in scintillation counters. Thallium has been alloyed with silver and with lead, has been used as a catalyst and included in fireworks. Thallium solutions have been used in mineralogical analysis. The industrial uses of thallium are at present limited, but may increase.

5. Environmental levels and exposures

5.1 General environment

Thallium is fairly widely distributed over the earth, mainly in rock formations, in very low concentration. It also occurs in potash, lead and zinc ores and in fossil fuels. Levels ranging from 0.3 to 3.0 mg/kg have been recorded in coal and 50 to 90 mg/kg in airborne material collected within 100 m of coal combustion sources (Natusch et al., 1973). Concentrations of 0.7 to 88 µg/liter were reported in river water draining a metal mining area in New Brunswick (Zitko et al., 1970). In algae and moss from these rivers concentrations ranging between 9.5 and 162 mg/kg dry weight were found. In Japan, thallium sulfate has been sprayed over forest areas to kill rats and other pests, but has not been found in samples of water taken over a period of one month after spraying (Kitayama and Saito, 1972).

The use of thallium to kill rodents implicates its spread to their natural predators such as foxes, weasels and martens. Furthermore, wild and domestic animals may feed on the poison directly.

Although pesticides containing thallium are no longer being sold in some countries, they can still be found stored in many homes. As a result of such storage, accidental contamination of food has occurred. Thallium has also been used in the past for therapeutic purposes, as for example to produce hair fall in the treatment of ringworm. Domestic contamination could therefore occur from stored medicines and ointments. Colorless and tasteless thallium compounds have also been used for homicidal purposes.

5.2 Working environment

Inhalation of thallium has resulted from the handling of flue-dusts and of dusts from the roasting of pyrites. Inhalational exposure may also occur in the extraction of the metal, in the manufacture of thallium-containing rodenticides, thallium-containing lenses and in the separation of industrial diamonds (Richeson, 1958). Glömme and Sjöström (1955) considered skin contact as the route of absorption of thallium in a group of workers manufacturing rodenticides.

6. Metabolism

6.1 Absorption

Absorption of thallium compounds is rapid following ingestion, inhalation or skin contact and may be complete following ingestion. In experiments on the rat, Lie et al. (1960) administered ^{204}Tl as a thallous nitrate solution by six different routes, oral, intratracheal, subcutaneous, intraperitoneal, intramuscular and intravenous. Whatever the route of administration, the body burden, as a proportion of the administered dose, was similar at any one time and followed a single exponential function extrapolating to 100 per cent at zero time. From these data, the authors deduced that complete absorption had occurred from the gastrointestinal tract following ingestion and from the respiratory tract following intratracheal injection. The rapidity of absorption from the gut of the rat was shown by Lund (1956) who observed thallium in the urine within one hour of oral administration of thallous sulfate.

6.2 Distribution

Thallium is widely distributed in the body following its rapid absorption in animals. Acute and chronic studies are in agreement that the highest concentration is found in the kidney. In the rat study reported above (Lie et al., 1960) the kidney concentration was 5 1/2 times the next highest concentration in the salivary gland. This was followed by testis, muscle, bone, lymph nodes, gastrointestinal tract, heart, spleen and liver all of which had relatively small differences in concentration between them. There was little variation in the relative thallium concentrations in these tissues on successive days during the first week, with the exception of hair. This latter increased with time so that after 21 days it contained up to 60% of the body burden. The relative organ concentrations remained constant whatever the route of administration. Blood contained very little thallium, indicating rapid equilibration with tissues. Thallium could not be detected in blood 20 minutes after injection and only in very low concentration two to three hours after intratracheal instillation. In chronic feeding experiments in the rat, Downs et al. (1960) found the highest concentration in the kidney, followed by bone, liver, lung, spleen and brain.

In man, too, thallium is widely distributed in the tissue, with the highest concentration in the kidney. However, the proportionate distribution has shown considerable variation. In the fatal case reported by Cavanagh et al. (1974) the second highest concentration was found in the heart. The concentration in grey matter was found to be three times that in white matter, although brain ranked low in order of tissue concentrations. Barclay et al. (1953) in their single case found the highest concentration in hair, followed by kidney and heart muscle.

6.3 Excretion

Thallium is excreted by the kidney and intestine, and also in small part by salivary gland, hair and into milk. It is also able to cross the placental barrier (Heyroth, 1947). In the rat study described above (Lie et al., 1960) excretion maintained a similar pattern regardless of the route of administration. Again, by whichever route thallium was administered, fecal exceeded urinary excretion during the 21 days of the study, the fecal to urinary ratio rising from 2 to 5, due to a gradual decrease in thallium excreted in the urine. Thyresson (1951) and Barclay et al. (1953) in observations in rats also found fecal excretion to exceed urinary. From observations in the rat following the intraperitoneal injection of 10 mg thallous sulfate per kg body weight, Lund (1956) found the principal routes for the elimination of thallium to be the gut and the kidney. Concentrations of the metal in gastrointestinal secretions corresponded with those in the plasma. In rabbits given an intravenous infusion of thallous nitrate, 0.5 g/l, thallium was shown to be excreted by glomerular filtration, about half the filtered amount being reabsorbed in the tubules. With the addition of 1% potassium sulfate to the infusion, the renal clearance of thallium was doubled, believed to result from the simultaneous tubular secretion of thallium and potassium (Lund, 1956). Rauws (1974) gave intravenous ^{204}TlSO$_4$ to a small group of rats and simulated thallium kinetics on the basis of a three-compartment model. He concluded that a significant exchange of thallium occurred between the tissues and the intestinal contents, which he described as an entero-enteral cycle.

Few observations have been made in man. Barclay et al. (1953) gave radioactive thallous nitrate and thallous sulfate to one patient with metastatic osteogenic sarcoma and found the rate of excretion in the urine to be 3.2% per day of the amount remaining in the body. Thallium excretion in both urine and feces may persist for many weeks in spite of low plasma levels in poisoned patients. In unexposed persons, the highest tissue concentration of thallium has been found in hair, throughout its length (Weinig and Zink, 1967) (See Section 7). In the long-term, therefore, hair and to a lesser extent nail, provides an important route for the slow excretion of thallium from the body.

6.4 Biological half-time

The body burden as a percentage of administered dose was determined in rats following the administration of ^{204}Tl by a variety of routes over a period of 21 days (Lie et al., 1960). Body clearance was found to occur exponentially with a half-time of 3.3 days whatever the route of administration. At the end of 21 days, the total period of observation, 1% of the administered dose remained. As, except for hair, there was no day to day variation in relative organ concentration, individual organs were considered to have similar biological half-times. With a biological half-time of 3.3 days, it was calculated that with daily dosing an equilibrium would be attained at about 20 days. In an industrial situation, assuming similar clearance rates in man, and with a five day per week exposure pattern, such an equilibrium may be attained in about 30 days.

A biological half-time of approximately four days was also found by Rauws (1974) in his observations with ^{204}Tl given intravenously in rats and quoted in Section 6.1. In his three compartment model, Rauws considered the brain as a compartment on its own, because of its role as a target organ and because thallium ions penetrate into it more slowly. He found the brain concentration to be always lower than the mean concentration in the organism calculated from body load and body weight.

7. Normal levels in biological tissues and fluids; indicators of exposure

Few data are available on levels of thallium in normal subjects. In a study on six people of various ages dying from unrelated causes, Weinig and Zink (1967) estimated tissue concentrations of thallium by mass spectroscopy. The highest values were found in hair, with concentrations ranging from 4.8 to 15.8 µg/kg. Concentrations in nail ranged from 0.72 to 4.93 µg/kg, and in the wall of the colon from 0.56 to 5.40 µg/kg wet tissue. The mean tissue concentration was calculated as 1.2 µg/kg, from which it was derived that the thallium content in a 75 kg person would be of the order of 0.1 mg. The same investigators found the thallium concentration in early morning urine samples in nine subjects to range from 0.13 to 1.69 µg/l. Johnson (1976) in a study in New Zealand on eleven subjects with no known exposure to toxic metals, found a mean thallium concentration in liver of 0.47 mg/kg dried tissue, with a range of 0.4 to 0.9 mg/kg.

Thallium concentration in tissues, urine, feces, hair and nails provides the only indicator of thallium exposure available at the present time. Weinig and Zink (1967) considered that no conclusion on poisoning in forensic practice could be drawn from tissue or urine levels of thallium less than 50 to 100 times their normal values, briefly quoted above.

8. Effects and dose-response relationships

8.1 Humans

Thallium compounds are cumulative in their effect and extremely toxic. In general, acute poisoning is characterised by gastroenteritis, with nausea, vomiting, diarrhea and abdominal pain within hours of absorption. Involvement of the nervous system then becomes apparent, with paresthesias, muscular pain and weakness, mental confusion or delirium, convulsions, respiratory and circulatory involvement followed by death. When the period of survival extends beyond one week or so, a varied neurological picture may develop with headache, ataxia, tremor, paresthesias and muscular atrophy predominating. There may also be cranial nerve involvement, with ptosis, retrobulbar neuritis or facial paralysis. After an interval of one to three weeks, alopecia develops, sparing pubic and axillary hair, and also the medial third of the eyebrows. Recovery may be complete or neurological defects may remain with mental abnormality, ataxia and tremor (Reed et al., 1963; Grunfeld and Hinostroza, 1964; Smith and Doherty, 1964; Matthews and Anzarut, 1968; Bank et al., 1972; Cavanagh et al., 1974).

Three cases, two of which were fatal, were described in detail by Cavanagh et al. (1974). The more acutely affected of these was initially diagnosed as a case of Guillain-Barré polyneuritis. This case showed little evidence of neuronal degeneration, but the second fatal case showed extensive distal degeneration of all nerve fibers examined, with chromatolysis of motor nerve cells. Neuronal degeneration was of the distal, dying-back type and was still continuing three weeks after the onset of paresthesia. In the second of Cavanagh's two fatal cases, the concentration of thallium in the kidney was 20 mg/kg; heart 13 mg/kg; brain (gray matter) 10 mg/kg; skin 6 mg/kg; liver, bone, muscle 5 mg/kg, with lower concentrations in other tissues. In the survivor, seven weeks after exposure, thallium could not be detected in the serum but was present in the urine in a concentration of 3.0 mg/l. In the fatal case reported by Smith and Duherty (1964), tissue thallium concentrations revealed 5.2 mg/kg of brain tissue, 7.8 mg/kg of kidney tissue, the bile contained 7 mg/l and the urine 2.29 mg/l. The fatal case reported by Grunfeld and Hinostroza had ingested more than 3 g thallium sulfate, probably the highest dose to be reported. Tissue concentrations in mg/kg were as follows: More than 20: colon and liver; 10-19: stomach, gallbladder, bone marrow, small bowel; 5-9: brain, lung, adrenal, spleen, cerebellum, kidney, muscle, pons, all in descending order.

The minimum lethal dose for soluble thallium salts for an adult is on the order of one gram thallium (Gettler and Weiss, 1943). The more acutely affected of the two fatal cases of Cavanagh et al. (1974) was estimated to have ingested 0.93 g Tl as the acetate in two divided doses, while the fatal case in which symptoms developed less rapidly had taken the same total amount but in 3 divided doses. The survivor had ingested 0.31 g Tl in a single dose. The so-called therapeutic dose, recommended to produce hair loss in two to three weeks, was 8 mg Tl/kg but Munch (1934) knew of six deaths in children given this dose, with evidence of poisoning in 5.5% of 8006 instances of therapeutic application. There is in fact no therapeutic dose for thallium salts. The minimum lethal dose for man is about 8 to 15 mg Tl/kg.

Thallium poisoning has occurred following the accidental contamination of food. In one outbreak, barley containing 1% thallium sulfate for pest control gave rise to 27 cases of poisoning with 7 deaths (Munch et al., 1933). Thallium salts have been used for suicide and their criminal use has been reviewed by Prick et al. (1955). Many cases of poisoning in children and adults, both fatal and with recovery, have followed the therapeutic use of thallium salts, especially in the treatment of ringworm. Of the 778 cases reviewed by Munch et al. (1933), 6 % were fatal.

Industrial thallium poisoning has occurred following absorption after inhalation of dust or fume, ingestion from contaminated hands or food or as a result of skin contact. Munch (1934) recorded 12 cases of industrial poisoning up to 1934. The principal clinical features in these cases were fatigue, anorexia, pains in the legs and loss of hair. There were no deaths, but one worker lost his sight with optic atrophy.

No information on doses is available. Glömme and Sjöström (1955) described 4 cases where absorption was thought to follow skin contact in the manufacture of rodenticides. Minor degrees of polyneuropathy and varying degrees of alopecia were noted, with maximal urinary excretion of thallium between 0.38 and 10 mg/l. Occupational thallium poisoning usually results from moderate, long-term exposure giving rise to a mild clinical course characterised by subjective symptoms, sometimes with polyneuropathy and with partial alopecia.

8.2 Laboratory animals

In acute poisoning the principal effects are seen in the digestive and nervous systems with, in addition, a necrotising renal papillitis. In chronic poisoning the most striking feature is loss of hair.

In chronic poisoning, the daily ingestion of thallium acetate added to the diet of male and female rats was tolerated at the 10 mg/kg level but was lethal in male rats at the 30 mg/kg level by 15 weeks (Downs et al., 1960). All rats fed an oral dose of 0.45 mg Tl/kg daily died after a period of 4 months (Manzlik et al., 1928).

8.3 Domestic and wild animals

Clausen and Karlog (1974) examined 60 wild martens and badgers in Denmark over a 2-year period and found a thallium load in 48% of these, with evidence of poisoning in 22% of the total. Acute hemorrhagic intestinal inflammation was seen in most of the cases of poisoning. In the 13 poisoned animals, liver concentrations ranged from 4.7 to 57 mg/kg; kidney concentrations ranged from 1.8 to 92 mg/kg and intestinal concentrations from 0.2 to 42 mg/kg. Thallium concentration was estimated in 34 red foxes in Denmark which had been found sick or dead during 1971 (Munch et al., 1974). In 4 out of 7 foxes where the cause of death could not be immediately established a thallium content was found in excess of 1 mg/kg in at least one organ. Of the 27 foxes where an alternative diagnosis had been made, thallium concentrations were greater than 1 mg/kg in 5; between 0.5 and 1 mg/kg in 8 and 0.5 mg/kg or less in the remaining 14 animals.

8.4 Interaction with potassium

There are similarities between the ions of thallium and potassium and there is experimental evidence to suggest that the biological handling of thallous and potassium ions is interrelated. Mullins and Moore (1960) found in frog muscle that potassium and thallium ions traversed cell membranes in a similar way, and Gehring and Hammond (1964) showed that the active transport mechanism for potassium into rabbit erythrocytes also transported thallium. These authors (1967) studied the relationship between the level of potassium and the excretion of thallium in rats, dogs and sheep. Infusion of potassium increased the renal clearance of thallium and also its mobilization from tissues. It was concluded from these experiments that the disappearance of thallium followed a first order kinetic process. However, while the ionic movements of thallium and potassium ions are related, once inside the cell, thallium appears to be less readily released than potassium. Thallium can substitute for potassium in causing activation of adenosine triphosphatase indicating that the mechanism involved in the active transport of potassium cannot differentiate between the two ions. In rats, an increased potassium intake increased the LD_{50} of thallium, suggesting a translocation away from the toxic receptor site (Gehring and Hammond, 1967). However, there is no clear evidence that the administration of potassium is beneficial in human thallium poisoning, although this is now generally advocated (Lancet, 1974). The excessive mobilization of thallium ions with subsequent redistribution in the tissues may even be detrimental (Cavanagh et al., 1974). Thallium has other effects on tissues in addition to those related to potassium transport (Truhaut, 1959).

9. Diagnosis, treatment and preventive measures

The diagnosis of thallium poisoning may be difficult because it is often unsuspected. The characteristic features are gastroenteritis, peripheral neuropathy and alopecia, the last occurring at a late stage. The possibility of thallium poisoning should be borne in mind in obscure neurological illnesses, especially where there is neuropathy, and thallium should be looked for in the urine. A brownish black pigmentation close to the hair root is characteristic of thallium exposure and may appear as early as the third or fourth day (Matthews and Anzarut, 1968; Gerdts, 1974).

The treatment of thallium poisoning is unsatisfactory and evaluation is difficult. Large doses of potassium chloride may hasten the excretion of thallium, but may cause a transient increase in blood levels and a redistribution in tissues which may lead to a temporary exacerbation of symptoms (Papp et al., 1969). In one case studied over a two-week period, the urinary concentration of thallium adjusted for specific gravity was directly related to the duration of the illness and unaffected by potassium chloride or by dithizone therapy (Smith and Doherty, 1964). Some authors have recommended hemodialysis and forced diuresis as effective in decreasing the body burden of thallium (Piazolo et al., 1971; Bank et al., 1972; Loew et al., 1972; Koch et al., 1972; Jax et al., 1973). Chelating agents have not in general been found to be useful (Smith and Doherty, 1964). Diethyldithio-carbamate has been shown to increase the urinary excretion of thallium in the rat (Schwetz et al., 1966), but Kamerbeek et al. (1971a) noted clinical deterioration and EEG disturbances coincident with administration in man. They observed increased levels of thallium in rat brain due to the formation of a lipophilic chelate. Kamerbeek et al. (1971b) reported increased fecal excretion of thallium with clinical improvement in 3 cases by giving Prussian blue (potassium ferric cyanoferrate II) by mouth, replacing the potassium ion in the Prussian blue molecule with thallium, thus rendering it unabsorbable from the gut. Van der Merwe (1972) reported a successful outcome in 2 patients treated with Prussian blue. Each had swallowed 700 mg thallous sulfate.

Rauws (1974) from his pharmacokinetic studies in the rat estimated a 70% inhibition of thallium reabsorption from the gut and considered this was responsible for the decrease of thallium half-time from 4 to 2 days in rats which had been pretreated with Prussian blue.

In the prevention of thallium poisoning in industry, substitution of less toxic compounds should be advocated wherever possible. Where thallium compounds must be used, strict safety precautions should be observed to prevent skin contact, inhalation or unwitting ingestion. Food, drink and cigarettes should be prohibited at the work site. With regard to poisoning in the community, the use of thallium-containing pesticides should be discontinued wherever possible and restrictions placed on their availability (Lancet, 1974).

10. Prognosis

The estimation of outcome in thallium poisoning is difficult. In general, cases with a fulminating onset are rapidly fatal, and the longer the course of the illness, the greater the chance of survival, although recovery may be incomplete where there is peripheral neuropathy. In one of the cases described by Grunfeld and Hinostroza (1964) the only manifestation of poisoning was nausea and vomiting of 16 hours' duration in spite of a urinary excretion of 1.65 mg Tl/l 5 days after ingestion.

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TIN

Magnus Piscator

1. Abstract

Inorganic tin compounds are absorbed to only a few percent from the gastrointestinal tract. Tin is mainly stored in bone, where the biological half-time in animals is about 100 days. Excretion is mainly via urine.

Organotin compounds vary in metabolism depending on number and type of organic radicals attached to the tin. Short chain alkyl compounds have a relatively high gastrointestinal absorption, whereas long-chain alkyl compounds are absorbed to a very small degree. Distribution, biotransformation and excretion differ among the organotin compounds.

Tin has not been shown to be an essential metal for humans. Experimental data indicate that 1-2 mg tin per kg diet promotes growth in rats.

The toxicity of tin after inhalation or dietary exposure is low. In exposed workers tin oxide accumulates in high concentrations in the lungs and causes "stannosis", a benign pneumoconiosis without tissue reaction or pulmonary dysfunction. Acute gastrointestinal disturbances have been common after ingestion of food packed in tin cans, especially acid juices. About 50 mg of tin may cause nausea and vomiting. Long-term exposure to smaller amounts has not caused any ill effects.

Some organotin compounds are highly toxic, especially triethyltin. Trialkyl compounds, especially triethyltin, cause an encephalopathy due to brain edema. Several deaths due to brain lesions have been reported among people treated with "Stalinon" a preparation containing diethyliodide contaminated with triethyltin. Triphenyltin compounds have caused liver damage in exposed workers. Long-chain alkyl compounds, e.g. octyltin,

There is no evidence that inorganic or organotin compounds can give rise to carcinogenic or teratogenic effects.

For further information, see reviews by Barnes and Stoner (1959) and Piver (1973). Both WHO and NIOSH are preparing criteria documents on tin; the latter will deal exclusively with organotin.

2. Physical and chemical properties

Tin, Sn, atomic weight 118.7; atomic number 50; density 5.8-7.3; melting point 231.9°C; boiling point 2260-2270°C; crystalline form, three variations: gray, cubic (tin gray), white metallic, tetragonal (tin white) and white rhombic (tin brittle); oxidation state 2, 4.

Transition from the gray allotropic form (α) to the white one (β) occurs when the temperature sinks below 13°C. The divalent compounds are designated as stannous and the tetravalent as stannic. At pH above 6, stannous compounds are easily oxidized. Tin does not occur in ionized form, but rather in colloidal complexes. In the organotin compounds, one to four carbon atoms may be bound directly to tin.

Tin forms a large number of inorganic and organic compounds. The inorganic tin compounds to be taken up here are tin oxide, tin tetrachloride, stannous chloride, stannic chloride, sodium chlorostannate, sodium pentachlorostannite, stannous fluoride and sodium pentafluorostannite. The organic compounds to be discussed include ethyl, butyl, octyl, phenyl, and cyclohexyl tin.

3. Methods and problems of analysis

The quantitative determination of small amounts of tin has always presented problems, as reflected in the large number of methods proposed. The merits of various methods have been difficult to evaluate owing to the lack of interlaboratory comparison.

There are many spectrophotometric methods available for the analysis of tin, among which are the dithiol, catechol violet and quercetin methods (Kirk and Pocklington, 1969; Adcock and Hope, 1970; Engberg, 1973). Atomic absorption is widely used at present for the determination of tin in different media. Most reports agree that the detection limit is not satisfactory, this being but one of several difficulties(Engberg, 1973). Tin oxide is not readily broken down in the flame, a problem which may be overcome to some extent by using special flame systems. This procedure may bring the limit of detection down to around 15 mg/l solution.Emission spectroscopy (Tipton et al., 1966), spark source mass spectrometry (Hamilton et al., 1972/1973a), neutron activation (Bowen, 1972) and X-ray fluorescence (Rudolph et al., 1973) have also been employed for analysis of tin in body fluids, tissues and food. The last three methods seem to be able to determine tin in concentrations of 1-100 µg/kg, but there are no interlaboratory comparisons available.

A variety of methods for identification and determination of organotin compounds is also available. Extraction steps, tedious and demanding great care, with solvents such as benzene and hexane, must often be performed to separate different organotin compounds before analysis. Chromatographic methods are generally used for the analysis itself (Fishbein, 1973).

4. Production and uses

4.1 Production

Tin is obtained mainly from cassiterite and to some extent from other ores in combination with other metals. In 1973 the total production of tin was more than 185,000 metric tons, Malaysia being the leading producer with 72,260 metric tons. USSR, Thailand and Indonesia are other important production countries in the eastern hemisphere. In the western hemisphere Bolivia is the main producer (28,568 metric tons). Tin is recycled to a considerable extent (Heindl, 1972).

4.2 Uses

Tin is used in tin plating (50%), solders and alloys, and in food cans (35%). Pewter, which contains 90-95% tin, 1-8% antimony and 0.5-3% copper, is widely used in trays, tankards, plates and the like (Heindl, 1972). Only about 4% serves for producing chemicals. Inorganic tin compounds play a role in a variety of processes from glass production to textile printing. Stannous chloride has been claimed to have a cariostatic action and has been added to toothpaste. Organotin compounds are used as stabilisers in plastics and as catalytic agents. Dioctyltin compounds are allowed as stabilisers in PVC plastics used for food wrapping. Triphenyl tin salts and many alkyltin compounds have been utilised as pesticides (Ross, 1965; Piver, 1973).

5. Environmental levels and exposures

5.1 General environment

5.1.1 Food and daily intake

In meat, cereals, and vegetables, concentrations of tin were usually less than 1 mg/kg in a study by Schroeder et al., (1964), using atomic absorption spectrophotometry. A diet based on such products was figured to give a daily tin intake of about 1 mg. In adults in the U.K. Hamilton et al. (1972/1973b) estimated an average daily tin intake of 187 µg. In meat, fats, cereals, and vegetables the concentration of tin averaged less than 0.1 mg/kg. Tipton et al. (1966, 1969) found an average daily intake of from 1.5 to 4.8 mg in long-term studies on 4 subjects. Estimates of the fecal output in the same study showed values from 1.6 to 4.6 mg. The daily intake of tin may be increased considerably if a good deal of canned food is eaten. The release of tin into canned food depends on many factors, such as presence of other chemicals, e.g. nitrates, pH and storage temperature (Bielig and Treptow, 1973). Canned tomato juice made from tomato plants treated with nitrate fertilizers has been linked with an outbreak of acute tin poisoning (Barker and Runte, 1972). Juices which have a high acidity may cause the release of tin from the plating resulting in very high concentrations, 100-500 mg/kg. The tin content of the stored food also increases considerably when an opened can is kept for a few days.

The risk for tin contamination may be reduced considerably by lacquering the cans (Bielig and Treptow, 1973). Still another source of an increased tin content in canned food is the use of stannous salts as additives. The stannous ion prevents other metals from being released and helps to maintain the ascorbic acid level.

Organotin compounds, e.g. dioctyltin, may be released into food from plastic bottles but the resulting concentration is generally less than 1 mg/kg (Carr, 1969).

5.1.2 Water, soil and ambient air

Several attempts to measure tin in various types of water have failed, probably due to analytical difficulties. When concentrations have been reported, they are usually around 1 µg/l or less. In municipal drinking water higher concentrations have sometimes been found. It has been suspected that some tin could be released into such systems from e.g. bronze fittings. It is not known whether organotin compounds occur to any large extent in water. Tin concentrations in soil vary greatly, from a few mg/kg to several hundred mg/kg (Schroeder et al., 1964). In sewage sludge Berrow and Webber (1972) found 40-700 mg/kg, on an average 160 mg/kg. In air, concentrations from < 3-300 ng/m^3 have been reported from the United States, the lowest values found in rural and suburban areas (Tabor and Warren, 1958). High volume samplers and a spectrographic method were used. In the Heidelberg area in Germany, Bogen (1973) reported levels around 100 ng/m^3; the method was neutron activation. At a distance of 700 m from an industrial plant, levels of 3.0-4.4 µg/m^3 have been recorded in Japan (Environment Agency, 1974).

5.2 Working environment

Exposure can be expected in the industries referred to in section 4. Oyanguren et al. (1958) found tin levels of 14.9 and 8.6 mg/m^3 near two respective foundry furnaces.

6. Metabolism

6.1 Inorganic tin

6.1.1 Absorption

6.1.1.1 Inhalation

There are no data from animal experiments or from studies on human beings on deposition or absorption of inhaled inorganic tin.

6.1.1.2 Ingestion

Studies on animals (Durbin et al., 1957; Kutzner and Brod, 1971; Hiles, 1974; Furchner and Drake, 1976) and on human beings (Calloway and McMullen, 1966) show that the absorption of ingested tin is only a few percent. In rats, Hiles (1974) estimated that the absorption of Sn (II) was about 4 times that of Sn (IV), 2.8 and 0.6% respectively.

6.1.2 Distribution

In animals given oral doses of tin the highest concentrations have been found in kidneys, liver and bone (Durbin et al., 1957; Hiles, 1974; Furchner and Drake, 1976). Most of the tin initially distributed to soft tissues was eliminated relatively rapidly therefrom. The main deposit of tin was in the skeleton which in one study contained 35% and 46% of administered doses of Sn (II) and Sn (IV) respectively two days after an injection (Hiles, 1974). Long-term oral administration of tin did not result in an accumulation in soft tissues, but the levels in bone were higher than after a single dose (Hiles, 1974). In human beings small amounts of tin have been found in most organs, mainly bone, lungs, liver and kidney. Tin has a tendency to accumulate in human lungs with age (Schroeder et al., 1964).

6.1.3 Excretion

Animal data (Durbin et al., 1957; Hiles, 1974; Furchner and Drake, 1976) indicate that injected tin is initially excreted mainly via urine, and to some extent via bile. About one-third of an injected dose of either Sn (II) or Sn (IV) was excreted via rat urine within 48 hours (Hiles, 1974). Durbin et al. (1957) found that rats excreted about 50% of a dose via urine and only 1% via feces 24 hours after injection. Thirty days after injection, altogether 20% had been excreted via the gastrointestinal tract, whereas the percentage excreted via urine remained the same. Furchner and Drake (1976) studied 5 species and found an average of from 19.8 % (mice) to 62.8 % (dogs) of the dose had been excreted via urine within 3 days after intravenous injection of ^{113}Sn (II) as the chloride. Via feces, from 5.6% to 10.6% had been eliminated within the same time period.

6.1.4 Biological half-time

Durbin et al. (1957) estimated the biological half-time in the rat after an injection of ^{113}Sn to be 84 days; the half-time in the skeleton was 100 days. Hiles (1974) estimated the half-time for Sn (II) in rat liver and kidney to be 10-20 days. In bone both Sn (II) and Sn (IV) had about the same half-time, 34 and 40 days respectively. In mice, rats, monkeys and dogs given intravenous or intraperitoneal injections of ^{113}Sn (II) Furchner and Drake (1976) found that the elimination could be described by four components, the longest one comprising 90-100 days.

6.2 Organotin compounds

Data are not available for many of the wide variety of organotin compounds. This lack is especially notable with regard to metabolism in human beings.

6.2.1 Absorption

6.2.1.1 Inhalation

There are no data from animal experiments or from studies on human beings on deposition patterns or absorption for inhaled organotin compounds.

6.2.1.2 Ingestion

The high oral toxicity of short-chain alkyltin compounds bears witness to their being absorbed. Quantitative data are available for monoethyltin chloride only. This compound is absorbed to about 8% in the rat as shown by Bridges et al. (1967). Triphenyltin acetate has been shown to be absorbed to about 10% in cows (Bruggemann et al., 1964) and in rats (Heath, 1963). Tricyclohexyltin chloride has an absorption of not more than 2% in the rat (FAO/WHO, 1971). No data are available for human beings.

6.2.1.3 Skin

Short-chain alkyltin compounds seem to be absorbed from the skin to a high degree, as indicated by their high toxicity after dermal application (Hall and Ludwig, 1972). Triphenyl compounds do not readily penetrate intact skin (Stoner, 1966).

6.2.2 Distribution

After injection of dibutyl- and diethyltin compounds, the highest concentrations were found in liver and kidney of mice and rats. After injection of triethyltin the highest concentration was found in the liver, with smaller amounts in kidneys and brain (Barnes and Magee, 1958). After three months of oral exposure, triethyltin was found mainly in liver, blood and muscles of rats, with minor amounts in kidney and brain (Barnes and Stoner, 1959). Species differences may be illustrated by the finding that triethyltin was absorbed in vitro by the red cells of rats, but not of rabbits (Barnes and Stoner, 1959). Triphenyltin, labelled with ^{113}Sn, has been found in liver, kidneys and brain both after injection and after oral exposure (Heath, 1963). After long-term oral exposure to tricyclohexyltin chloride, labelled with ^{119}Sn, minor amounts were found in the brain, kidney, liver, and muscles of rats (McCollister and Schober, 1975). In a two year study, dogs and rats were given tricyclohexyltin chloride orally. In the dog, the highest concentrations were in liver, kidney and brain.

6.2.3 Excretion

The excretion pattern of triethyltin is not known in detail but it seems that only a minor part is excreted via kidneys. It has been shown that diethyltin is excreted via the bile and monoethyltin via the urine (Bridges et al., 1967). Triphenyltin has a relatively slow excretion, mainly via urine.

In milk from exposed sheep only minor amounts of tin were found (Herok and Götte, 1964). Tricyclohexyltin is excreted slowly but the major route is not known.

6.2.4 Biological half-time

For triphenyltin, the biological half-time in rat brain has been estimated to be about 3 days, but it seems to be considerably longer in the guinea pig (Heath, 1963). The half-times for tricyclohexyltin compounds in different rat tissues have been reported to vary from 5 to 40 days, the longest half-time being in the brain (FAO/WHO, 1971). There are no data on half-times for alkyltin compounds.

6.2.5 Biotransformation

Tetraethyltin is metabolized to triethyl, and probably also to di- and monoethyl, tin compounds (Cremér, 1957, 1958). These processes are governed by enzymes in the microsomes of the liver (Casida et al., 1971). Diethyltin is transformed to monoethyltin in the gut (Bridges et al., 1967). In sheep exposed to triphenyltin, about 90% of the tin in milk was in organic form while about 10% was in inorganic form. There are no data on biotransformation of tricyclohexyltin compounds.

7. Normal levels in tissues and biological fluids

The average concentration of tin in whole blood, determined by spark source mass spectrometry, was about 5 µg/l (Hamilton, 1972/73b) which is considerably lower than values reported earlier by Kehoe et al. (1940), i.e. 140 µg/l more than 80% of which was in the cells. Kehoe et al. employed a colorimetric method. Rudolph et al. (1973), using X-ray fluorescence, found 37 µg/l in serum, which better agrees with Kehoe et al.'s old data. Conclusions as to the true levels of tin in human blood are not permitted by available data. The urinary excretion of tin has been reported to be around 20 µg/day in three studies (Kehoe et al., 1940; Perry and Perry, 1959; Meltzer et al., 1962).

In tissues the concentrations of tin are generally less than 1 mg/kg. The highest concentrations have been found in bone (ribs), lungs, liver and kidney, i.e. 0.8, 0.8, 0.4 and 0.2 mg/kg wet weight respectively (Hamilton et al., 1972/73b). These data agree well with earlier data by Kehoe et al. (1940) who found 0.5, 0.45, 0.6, and 0.2 mg/kg wet weight in the respective organs.

8. Effects and dose-response relationships

Tin has not been shown to be an essential element in human beings. It has been claimed that 1-2 mg tin/kg diet is necessary for growth in rats (Schwarz, 1974).

8.1 Inorganic tin

8.1.1 Local effects and dose-response relationships

8.1.1.1 Animals

Gastric irritation occurred in cats given canned fruit juices contaminated with soluble tin salts (Benoy et al., 1971). Eleven cats given orange juice containing 498 mg/l of tin did not vomit whereas one of 11 vomited when the tin content was increased to 540 mg/l. The doses per kg body weight were 2.5 and 2.7 mg. A concentration of 1370 mg/l, 14 mg/kg body weight, induced vomiting in three out of ten cats. This dose did not induce vomiting in dogs.

Inhalation exposure for 10 minutes to tin tetrachloride at a concentration of 3 g/m^3 was said to be well tolerated by guinea pigs. Even repeated exposure to this concentration was claimed to be tolerated (Pedley, 1927). There are no later data that can support these statements.

8.1.1.2 Humans

Several outbreaks of food poisoning due to tin contamination in canned food have been reported, see e.g. Benoy et al. (1971). The lowest concentration reported to have caused effects (nausea, vomiting and diarrhea) is 250 mg/kg (Benoy et al., 1971). Svensson (1975) examined 85 persons who had consumed contaminated canned peaches and estimated the doses that had given rise to effects. The concentration of tin was 413-597 mg/kg peach, and 398 mg/l syrup. The pH was 3.9. Of 78 persons who had consumed 100 mg tin or more, 74 showed symptoms, whereas 2 out of seven who had consumed 50 mg were affected. Nehring (1972) reported that canned peaches containing 563 mg tin/kg had caused gastrointestinal symptoms. Acute gastroenteritis was seen in 113 persons who had consumed tomato juice containing 400 mg tin/l (Barker and Runte, 1972).

Five volunteers given canned juice with a pH of 3.9 and containing about 500 mg tin/l (1.59-2.65 mg/kg body weight) did not show any symptoms. A concentration of 1370 mg/l (4.38-6.71 mg/kg body weight) did result in gastrointestinal disturbances in the same study (Benoy et al., 1971). No effects were seen in volunteers after long-term consumption of canned food containing about 200 mg/kg of tin (Calloway and McMullen, 1966).

No acute effects have been ascribed specifically to the inhalation of tin, but "stannosis", a benign pneumoconiosis caused by long-term exposure to tin oxide dust or fumes, has been reported in several studies (Pendergrass and Pryde, 1948; Cutter et al., 1949; Dundon and Hughes, 1950; Schuler et al., 1958; Oyanguren et al., 1959). In none of these studies has there been any evidence of a decreased pulmonary function.

Stannosis appears on the radiograph as small shadows, denser than those of silicosis. The first sign is an increase in bronchovascular markings and hilar thickening. A fully developed stannosis was observed after 3-5 years of exposure to tin oxide fumes in a foundry. The concentrations in air near two furnaces were 14.9 and 8.6 mg/m^3 respectively (Schuler et al., 1958; Oyanguren et al., 1958).

A man who died 18 years after his last exposure to tin oxide fumes and who had stannosis without respiratory dysfunction was found to have 7,100mg tin/kg wet weight in the lungs upon autopsy. This concentration is more than 1,000 times the "normal". No tissue reaction to this high concentration had taken place. Tin was identified in the oxide form (Dundon and Hughes, 1950).

8.1.2 Systemic effects and dose-response relationships

8.1.2.1 Animals

Injected tin compounds have been shown to cause paralysis and other signs of neurological damage in several species (see review by Barnes and Stoner, 1959). Conine et al. (1975) observed neurological damage and renal lesions in rats exposed to stannous chloride. A subcutaneous dose of 28 mg tin/kg as stannous chloride increased heme oxygenase activity in the kidney of rats 20 to 40-fold (Kappas and Maines, 1976). Long-term studies have been carried out by Schroeder and Balassa (1961) and Schroeder et al. (1968) in which mice and rats were given tin as stannous chloride in drinking water (5 mg/l) from weaning to natural death. In mice no gross effects were noted, but in female rats a reduced longevity and an increased incidence of fatty degeneration of the liver were reported.

Special interest has been devoted to sodium pentafluorostannite owing to the reported anticariogenic activity. In a 30-day study on rats, sodium pentafluorostannite in a concentration of 20 mg/kg diet (13 mg Sn/kg) had slight toxic effects, indicated by a tendency toward reduced weight gain. Higher doses resulted in renal damage, attributed mainly to fluoride (Conine et al., 1976).

A 90-day toxicity study on rats given tin compounds orally disclosed a no-effect level of 22-33 mg tin/kg body weight per day. At higher levels anemia appeared, which could be alleviated by increased dietary iron (de Groot et al., 1973).

8.1.2.2 Humans

In the study by Calloway and McMullen (1966) nine volunteers were given canned food from military rations with tin concentrations of 13, 33 and 204 mg/kg respectively for three 24-day periods. No toxic effects were noted. Absorption of iron tended to increase when 204 mg tin/kg food was given, which might have a bearing on the findings by de Groot et al. (1973) mentioned in the previous section.

8.2 Organotin

8.2.1 Local effects and dose-response relationships

8.2.1.1 Animals

Large single oral doses (4000 mg/kg) of some monobutyltin compounds produced gastrointestinal damage (Pelikan and Cerny, 1970). Similar damage was seen after oral administration of tributyl compounds (Pelikan and Cerny, 1968a). Some tributyltin compounds caused skin irritation in rabbits at concentrations of 0.36 to 0.95 mg/kg. High concentrations caused marked inflammation and skin necrosis (Pelikan and Cerny, 1968b).

Triphenyltin hydroxide was reported not to irritate rabbit skin, but was extremely irritant to the eye (Marks et al., 1969). Klimmer (1964) found that a 10% solution of triphenyltin acetate in oil in a dose of 150 mg/kg body weight gave a skin reaction in rats.

8.2.1.2 Humans

In workers handling dibutyltin and tributyltin chlorides skin lesions, even burns, have been found (Lyle, 1958). The irritant effect appeared between 1 and 8 hours after contact. Healing was rapid after removal from exposure. The eyes can also be affected, as seen in a case described by Lyle (1958) but this damage was not chronic.

Triphenyltin acetate caused skin and eye irritation in workers, but the symptoms disappeared without treatment when exposure ceased (Markicevic and Turko, 1967). Application of 0.5 ml of a 0.1% emulsion of tricyclohexyltin hydroxide two times with an interval of 20 days did not produce any skin reaction or sensitization in 53 women (FAO/WHO, 1971).

8.2.2 Systemic effects and dose-response relationships

8.2.2.1 Animals

Concerning the alkyltin compounds the highest toxicity is found among the short-chain trialkyl compounds, i.e. trimethyltin and triethyltin. The toxicity declines as the number of carbon atoms in the chain decreases. The trialkyl compounds are generally more toxic than the dialkyl and monoalkyl compounds (Barnes and Stoner, 1958; Klimmer, 1969).

After injection or oral exposure organotin compounds have caused a wide variety of symptoms. Triethyltin compounds produce an encephalopathy characterised by an edema of the white matter, while the nerve cells do not suffer damage. This lesion is distinct from brain lesions produced by other alkyl metals, i.e. alkyl lead and alkylmercury. The lesion, which is reversible, could be produced by an intravenous dose of 4 mg/kg in the rabbit (Magee et al., 1957) as well as by an oral exposure to in rats.

Other trialkyl compounds had a weaker effect on the brain (Barnes and Stoner, 1958). Dioctyltin produced no effects when given to rats in a concentration of 200 mg/kg diet for 4 months (Barnes and Stoner, 1958). Tri- and dibutyltin compounds caused mainly liver and bile duct lesions respectively (Barnes and Magee, 1958; Pelikan and Cerny, 1968a).

Triphenyltin compounds gave rise to effects in liver, kidneys and central nervous system. The no-effect level for triphenyltin acetate in a 2-year study on rats was found to be 0.1 mg/kg/day (FAO/WHO, 1971).

Intraperitoneal injections of 10 mg/kg and higher of tricyclohexyltin hydroxide caused neurological damage in rats (McCollister and Schober, 1975). The no-effect level in rats has been estimated to be 3 mg/kg/day in a 2-year study (FAO/WHO, 1971, 1974). In dogs it was found to be 0.75 mg/kg/day.

8.2.2.2 Humans

In 1954 more than 100 deaths and more than 200 cases of illness occurred in France due to the ingestion of a preparation (Stalinon) containing diethyltin diiodide, 15 mg per capsule, for treatment of furuncles, acne and some other disorders (Alajouanine et al., 1958; Barnes and Stoner, 1959). The preparation also contained monoethyltriiodide and triethylmonoiodide, the concentration of the latter comprising about 10% of the diethyltin compound. The total dose of ethyltin compounds over a period of 6 to 8 weeks was calculated to be 3 g. The doses of diethyltin were estimated to be from 45 to 675 mg in non-fatal cases and from 360 to 675 mg in fatal cases (Barnes and Stoner, 1959).

Symptoms appeared in some cases after only a few days of treatment and consisted of severe headache, vomiting, vertigo and visual disturbances. Meningism, paresis and convulsions were sometimes present, but physical signs could be absent even in some fatal cases. There were no consistent alterations in encephalograms. Death occurred from coma, respiratory or cardiac failure. In fatal cases a pronounced edema of the white matter of the brain was seen (Gruner, 1958). In non-fatal cases recovery was slow and neurological signs were noted up to four years after exposure. There have been no reports on further follow-ups. Even though triethyltin iodide is strongly suspected as being the causative agent, no report has shown this conclusively.

Prüll and Rompel (1970) reported headaches, nausea and visual disturbances in five workers with acute intoxications from organotin (compound not stated, but presumably triethyltin). Electroencephalograms showed general disturbances, dysrhythmia, and involvement of the occipital cortex.

Liver damage, in one case irreversible, has been reported in people using triphenyltin acetate as a spray (Horacek and Demcik, 1970; Mijatovic, 1972). Exposure to other toxic compounds cannot be excluded.

8.3 Carcinogenic and teratogenic effects

Roe et al. (1964) gave rats inorganic tin compounds via food for 80 weeks. One group (n = 37) received sodium chlorostannate, 20,000 mg/kg,one group (n = 37) received stannous 2-ethyl hexoate, 10,000 mg/kg, and one group (n = 40) served as controls.

In the first group, 3 malignant tumors developed among the 30 rats surviving more than one year, whereas no malignant tumors were seen in the other two groups. The small number of animals makes it difficult to draw any conclusions.

Kanisawa and Schroeder (1967) gave stannous chloride in drinking water, 5 mg/l, to 108 mice for their life-times. The control group consisted of 198 animals. 86 and 170 autopsies were performed in the two groups whereupon 15 and 6 malignant tumors, respectively, were found.

Triphenyltin acetate was not found to be carcinogenic in an 18 month study on mice (n = 72). The daily dose via food was 0.46 mg/kg body weight (Innes et al., 1969).

Tricyclohexyltin hydroxide given to rats in daily dietary doses of 12 mg/kg body weight for 2 years did not cause an increased incidence of tumors (FAO/WHO, 1971).

Teratogenic effects were not seen in pregnant rats given sodium pentafluorostannite, sodium pentachlorostannite and stannous fluoride corresponding to tin levels of 125-500, 125-500 and 156-625 mg/kg respectively. In control fetuses the tin concentration was 0.64 mg/kg while in the exposed it varied from 0.81 to 1.28 mg/kg, indicating a slight placental transfer (Theuer et al., 1971).

FAO/WHO (1971) has evaluated studies on tricyclohexyltin hydroxide. A 3-generation study on rats using an exposure of 100 mg/kg diet did not reveal any effects on reproduction or on fetuses. In rabbits given 3 mg/kg/day via food from day 8 to 16 of gestation, no effects were seen. With regard to triphenyltin, the data are conflicting. Effects on the testes and ovaries were brought about in two studies on rats given 20 mg/kg/day of triphenyltin acetate or chloride for less than 4 weeks. On the other hand no effects on the testes were found in three studies when up to 25 mg/kg diet was given to rats (FAO/WHO, 1971). Gaines and Kimbrough (1968) found a reversible fertility reduction in male rats given 200 mg/kg diet for 9 months. No abnormalities were noted in the next generation.

In a 6-month study, an increase in chromosome aberrations in bone marrow cells was found in rats given gastric doses of 0.1 mg/kg of dibutyltin sulfide (Mazaev and Shlepnina, 1973).

8.4. Mechanisms of action

There are no data on the action of inorganic tin. The extensively studied triethyltin has been shown to have a strong affinity to mitochondria, where it binds to histidine and inhibits oxidative phosphorylation (Aldridge, 1958; Rose, 1969; Aldridge and Street, 1964, 1970, 1971). Other trialkyl compounds cause similar effects.

In vivo studies in the rat brain showed that triethyltin inhibited glucose oxidation (Cremer, 1970). The dialkyl compounds, with the exception of dioctyl, affect the mitochondria by inhibiting the oxidation of 2-keto acids (Piver, 1973).

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TITANIUM

Maths Berlin

1. Abstract

Titanium compounds common in the environment are little absorbed upon ingestion and inhalation. Detectable amounts of titanium can be found in blood, brain and parenchymatous organs; the highest amount is seen in the lung, probably due to retention of titanium-containing dust particles. Excretion occurs via urine and feces. Data on biological half-time are not available at present.

There is no evidence that titanium has any physiological metabolic function. Most animal and human data indicate a low degree of toxicity for common titanium compounds. However, in animal experiments, titanium carbide, nitride and hydride have been observed to cause liver and kidney as well as heart damage. Organic titanium compounds have been shown to produce cancer in animal experiments. Long-term administration of soluble titanate has disturbed reproduction in animal experiments.

2. Physical and chemical properties

Titanium, Ti, atomic weight 47.9; atomic number 22; density 4.5; melting point 1660°C± 10; boiling point 3287°C; crystalline form α hexagonal, transition point β cubic 838, silver-gray; oxidation state +2,+3,+4.

Titanium has both metallic and non-metallic characteristics and occurs mostly in a tetravalent form, titanic, but trivalent, titanous, and bivalent forms are known, in addition to oxyforms such as $TiOCl_2$, titanyl chloride. Several other inorganic compounds which are referred to in this chapter are titanium oxide, titanium tetrachloride, titanous chloride, titanium dioxide, titanium carbide, titanium halide, titanium nitride, barium tetratitanate, titanium hydride, titanic acid, titanic oxychloride, titanium oxalate, titanium acetate, titanium salicylate, titanium tannate, titanium boride. The metal is highly resistant to many corrosive agents, including concentrated nitric acid. A number of organometallic compounds with titanium are known, for example titanocene; the most common are the alkyl and aryl titanates of the general formula $Ti(OR)_4$. Complex organic coordination compounds of titanium are also known.

3. Methods and problems of analysis

For the determination of titanium in air, water, food and biological material, a wide variety of analytical procedures has been employed, such as spectrography (Durum and Haffty, 1961; Eremenko and Mel'Nikov, 1968; Timakin and Bagdasarova, 1969; Chekotilo and Torokhtin, 1970), photometry (Schlenk, 1936; Yound and White, 1959; Loiko, 1967; Urusova, 1969; Mal'Tseva, 1973a; Mal'Tseva, 1973b), atomic absorption (Beyer, 1969; Burnham et al., 1970; Carlson and Black, 1970; Hwrng, 1972; Ranweiler and Moyers, 1974), atomic fluorescence spectrometry (Schiller, 1970; Slavin and Manning, 1963; Kirkbright et al., 1969; Chakrabarti and Katyal, 1971; Ottaway et al., 1970), X-ray fluorescence (Shono and Shinra, 1969; Dittrich and Cothern, 1971; Rhodes et al., 1972; Frigieri et al., 1972; Blasius et al., 1972), spark source spectrography (Crocker and Merritt, 1972; Hamilton and Minski, 1972; Hamilton et al., 1972/1973), neutron activation (Dams et al., 1970; Zoller and Gordon, 1970; Harrison et al., 1971; Dams et al., 1972), polarography (Hoff and Jacobsen, 1971; Petit, 1973), and proton-induced X-ray emission spectrometry (Johansson at al., 1972, 1974). A practical limit of detection of about 1 ng for titanium in air has been achieved by PIXE spectroscopy (Johansson et al., 1972,1974). The same method has been adapted for water and has a detection limit of less than 1 ng/drop of water (Johansson et al., 1972). The detection limit for titanium assay in human tissue by spark source mass spectrometry was 0.067 g/kg (Hamilton et al., 1972/1973) and by X-ray fluorescence 0.3 g/kg (Hamilton et al., 1972/1973).

4. Production and uses

4.1 Production

Titanium is the eighth most common element in the earth's crust and occurs in a number of minerals. The major titanium minerals commercially mined are ilmenite and rutile. From these minerals, the yearly world production of titanium oxide is about 1.5 million tons, and it is estimated to be doubled by the year 2000.

4.2 Uses

Titanium metal has extensive applications in aerospace, including aircraft and spacecraft. Because of its resistance to corrosion and its inertness, titanium is widely used in the chemical industry for tubing and for lining vessels in production of nitric acid and acetaldehyde. It is also used in the paper pulp industry. Titanium metal may be a component of surgical implant material or prothesis. Titanium dioxide is the most common titanium compound used because of its extreme whiteness and brightness as well as its high index of refraction. It is extensively used as a white pigment in paints, lacquers, enamels, paper coatings and plastics.

Titanium oxide is also used as a color additive in confection, dairy products and bread flour, replacing the flour bleaching agent normally used. It serves as a clouding agent for incorporation into dry beverage mixes, and in tobacco wrapping and tobacco substitutes. Due to its effectiveness as a shortwave ultraviolet sun screen, titanium oxide is included in a variety of drugs and cosmetics. Another commercially important compound of titanium is titanium tetrachloride, used as an intermediate in the production of titanium metal and titanium pigments but also as a component and catalyst in the chemical industry. Titanous chloride, $TiCl_3$, is prepared by reducing titanium tetrachloride. This compound is also used as a polymerization catalyst. Organic titanium compounds are used as cross-linking agents and catalysts in chemical processes.

5. Environmental levels and exposures

5.1 General environment

5.1.1 Food and daily intake

Titanium is poorly absorbed and retained by plants and animals

(Monier-Williams, 1950; Underwood, 1971). Levels of around 1 mg/kg dry weight have been reported for a wide variety of plants (Mitchell, 1957). However, local contamination by fly-ash fallout or fertilization of titanium-containing sewage residues as well as the use of titanium dioxide as a food whitener may cause higher levels of titanium in food products. Schroeder et al. (1963) found titanium levels from 1.76 to 2.42 mg/kg wet weight in milled grains, butter, corn oil and vegetables, especially lettuce. Wheat flour from the US and Japan was found to contain 0.41 and 0.99 mg/kg titanium respectively. Certain types of cheese contain high concentrations of titanium due to the addition of titanium dioxide to whiten the cheese and to accelerate aging (Palo, 1966, 1967; Kosikowski and Brown, 1969; Leone, 1973).

More than 99% of the total daily intake comes from food and water, and the daily intake from water is low, around 2 μg (Schroeder et al., 1963). The daily intake from food will vary widely with food habits. Typical American diets have been estimated to contain between 3-600 μg of titanium (Schroeder et al., 1963; Poole and Johnston, 1969). The daily intake from air of titanium has been estimated for American cities (Woolrich, 1973) to be around 4 μg, which constitutes a few tenths of a percent of the total daily intake.

5.1.2 Water, soil and ambient air

Titanium concentrations between 2-107 μg/l have been reported for fresh water in the US and Canada (Durum and Haffty, 1961). Drinking water in the US contains around 2 μg/l, range 0.5-15 μg/l (Durfor, 1963). Titanium concentration in sea water is mostly around 0.6-1 μg/l; values up to 9 μg/l have been reported (Mason, 1958; Bowen, 1966; Ishibashi, 1966; Silvey, 1967).

Soil generally contains between 0.3-6% titanium (Vinogradov, 1959; Monier-Williams, 1950). However, there are many soils with an exceptionally high titanium content, up to 10% (Vinogradov, 1959; Chilean Nitrate Educational Bureau, 1958).

Soils in the vicinity of power incineration plants may be enriched with titanium.

Atmospheric levels of titanium between 0.01-0.5 μg/m^3 in soots and dust have been reported (Tabor and Warren, 1958; Japan Environmental Sanitation Center, 1968) with about 2-10 times higher concentration over urban areas compared to non-urban areas.

5.2 Working environment

Occupational exposure to titanium is mainly found in mining, production of titanium metal dioxide or carbide. Titanium exposure is mainly in the form of dust but in connection with handling titanium tetrachloride, fume and vapor exposures occur. Concentrations of titanium compounds in air between 20-50 μg/m^3 have been reported by several authors (Mogilevskaya, 1972, 1973; Mezentseva, 1967) in connection with dusty operations.

6. Metabolism

6.1 Absorption

Data on absorption of titanium compounds are very limited. Titanium dioxide has been shown to be absorbed to a very low degree in animal experiments. Rats, given 250 mg/kg in the diet, excreted more than 90% of the daily intake in feces (Fournier, 1950). In mice, given 5 mg/kg titanium as a soluble salt during their entire life span, a five times increase in organ content of titanium, as compared to control animals, has been observed (Schroeder et al., 1964).

In humans, about 10 μg/l of titanium is found in urine, which suggests a titanium absorption of about 3% assuming an intake of 700 μg/day (Perry and Perry, 1959; Schroeder et al., 1963). Data on absorption by inhalation are not available. Data on metabolism and excretion of titanium are lacking for the most part. As mentioned above, titanium in about 10 μg/l is regularly excreted in urine in man.

The mechanism of excretion and the possible amount excreted by the intestinal route are unknown.

6.2 Distribution

Studies on mice given titanium in food during their life span have shown the presence of between 2 and 9 μg of titanium in parenchymatous organs such as heart, lung, spleen, liver, and kidney (Schroeder et al., 1964). In man, the highest titanium concentration has been found in lung (Tipton and Cook, 1963), probably as a result of inhalation of titanium particles. Detectable levels have also been found in blood, brain, and other parenchymatous organs (Hamilton et al., 1972/1973). In blood, distribution of titanium between erythrocytes and plasma has a ratio of 2:3 (Smyshlyaeva et al., 1971).

6.3 Biological half-time

There are no studies available providing a basis for an estimate of biological half-time in man or animals.

7. Normal levels in tissues and biological fluids

Levels between 0.03-0.15 mg/kg of titanium in blood have been reported (Maillard and Ettori, 1936a; Maillard and Ettori, 1936b; Timakin et al., 1967; Hamilton et al., 1972/1973). Concentrations of 3.7 mg/kg have been reported in the lung, and 0.8 mg/kg in the brain (Hamilton et al., 1972/1973). In coal miners, considerably higher levels of titanium have been reported in the lung (Crable et al., 1967, 1968).

8. Effects and dose-response relationships

The most common forms of titanium used in present-day communities are titanium metal and titanium oxide. These forms have a low toxicity as shown in experimental animals and in observations on exposed humans. Titanium halides have been shown to be irritant to the respiratory tract (Stokinger, 1963). Titanium nitride has been observed to cause dystrophy of the liver and the renal tubular epithelium as well as some fibrogenetic activity in the lung in exposed animals (Brakhnova and Samsonov, 1970). Titanium boride and titanium carbide have also been observed to cause fibrogenic action in the lung and dystrophy of the liver and kidney as well as of the myocardium (Brakhnova, 1969). In rats, titanium metal powder, injected intramuscularly, has been observed to cause fibrosarcomas and lymphosarcomas (Furst, 1971), and an organic titanium compound, titanocene (Furst, 1971; Furst and Haro, 1969), has been shown to be carcinogenic if injected intramuscularly to rats, causing fibrosarcomas at the injection site, hepatomas and malignant lymphomas of the spleen. Most data on toxicity of titanium compounds are derived from animal experiments. Epidemiological and clinical observations on humans have not yet revealed any significant toxic effects of titanium compounds used in industry.

8.1 Local effects and dose-response relationships

8.1.1 Animals

8.1.1.1 Short-term studies

Intratracheal injections of titanium oxide, 20-50 mg to rats (Mogilevskaya, 1956; Göthe and Swensson, 1970) and up to 400 mg to rabbits (Dale, 1973) have not shown anything other than non-specific reactions to dust particles. Intratracheal instillation of other titanium compounds such as barium tetratitanate, 5% suspension in saline, to guinea pigs and in 50 mg doses as a dust to rats, have not produced signs of fibrotic reaction (Pratt et al., 1953). A weak fibrogenic effect was seen after administration of 50 mg of titanium hydride to rats (Brakhnova and Shkurko, 1972). Rats exposed to hydrolysis products of titanium tetrachloride by inhalation for two hours at concentrations from 0.1 to 3 mg/l showed fatal injuries in a frequency decreasing with decreasing concentration. Mortality was significantly higher than in groups exposed to equivalent amounts of hydrochloric acid vapor (Mezentseva, 1967).

8.1.1.2 Long-term studies

Implantation of titanium metal in dogs (Beder et al., 1941; Gross and Gold, 1957; Shpak and Margolin, 1971) has shown that soft tissue has a high tolerance to titanium metal, illustrated by lack of irritation, good wound healing and the incapsulation of the metal by fibrous tissue. Rats, which inhaled titanium oxide dust four times daily five days a week up to 13 months, did not show any pathological responses in the lungs seven months following cessation of exposure. In guinea pigs fibrotic effects and eosinophilic infiltrations have been observed after repeated titanium oxide inhalation over various time intervals from five days to four months (Lensi, 1936). Intratracheal injections to rats of a suspension of 50 mg metallic titanium dust or titanium oxide dust, particle diameters less than 2 μ, did not show any fibrosis six months or eleven months after injection (Mogilevskaya, 1956). Weak fibrogenic effects were, however, observed when titanium hydride was inhaled by rats for 1-6 months (Shkurko and Brakhnova, 1973).

8.1.2 Humans

Vernetti-Blina (1928) studied men exposed to titanium oxide for prolonged periods. These studies did not reveal any signs of clinical or radiological abnormality. Uragoda and Pinto (1972) investigated the health of 136 workers exposed to ilmenite and rutile in Ceylon. No significant differences in the incidence of radiological lesions of the chest were seen in these workers as compared to the general population. Lung specimens from three factory workers exposed for nine years in processing titanium oxide pigments were examined by Elo et al. (1972). Deposits in pulmonary interstitium with cell destruction and slight fibrosis were seen. Titanium oxide particles were found in the lymph nodes, suggesting clearance via the lymphatic system. The authors characterized titanium oxide as a mild pulmonary irritant. Splashing with titanium tetrachloride at 100°C and inhalation of fumes of titanic acid and titanic oxychloride led to surface skin burns with scarring (Heimendinger and Klotz, 1956). Congestion of the mucous membranes of the pharynx, vocal cords and trachea, with cicatrization as a late sequel with laryngeal stenosis, was also observed.

8.2 Systemic effects and dose-response relationships

8.2.1 Animals

Intraperitoneal injections of 25-250 mg/kg body weight to rats (Huggins and Froehlich, 1966; Sethi et al., 1973) did not give rise to other changes than could be expected from inert particles. Titanium nitride (Brakhnova and Samsonov, 1970), boride, carbide (Brakhnova, 1969) and hydride (Shkurko and Brakhnova, 1973) have been observed to cause dystrophy of the liver and renal convoluted tubules.

8.2.2 Humans

No data on dose-response or dose-effect relationships concerning systemic changes caused by titanium compounds in humans are available. Lack of toxicity of titanium and its compounds from contact with skin and tissues has been demonstrated by its use in therapy of skin disorders and in surgical appliances (titanium salicylate, oxide and tannate).

8.3 Carcinogenic effects; teratogenic effects and effects on reproduction; genetic effects

Carcinogenicity studies were performed on 50 rats with titanium metal powder (Furst, 1971). Increased rates of fibrosarcomas and lymphosarcomas were observed in rats which survived up to 820 days compared to controls. Titanium oxalate and acetate, 5 mg/l in drinking water, from weaning to death, were non-carcinogenic in 150 mice of both sexes as compared to control groups (Schroeder et al., 1964). The organic compound, titanocene (Furst, 1971; Furst and Haro, 1969), has been shown to be carcinogenic when suspended in trioctanoin and injected intramuscularly to rats and mice. Fibrosarcomas occurred at injection site and the animals developed hepatomas and malignant lymphomas of the spleen.

In reproduction and teratogenicity studies, Schroeder and Mitchener (1971) found a toxic effect of a soluble titanate on the reproduction of mice and rats given 5 mg/l of the compound in drinking water. Each group was followed through three generations. In the rats, marked reduction in the numbers of animals surviving the third generation appeared, and the male-female ratio was progressively reduced compared to the controls, which continued to breed for four generations at a normal rate. Titanium salts have been reported to induce sticky chromosomes in root stems of allium cepa (Levan, 1945).

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TUNGSTEN

George Kazantzis

1. Abstract

In the rat, following ingestion in the form of tungstate, almost one half of the administered dose of ^{185}W was rapidly absorbed into the plasma and the greater part of it was rapidly excreted by glomerular filtration. Transfer occurred to red blood cells and, following sequestration, to the spleen which accumulated the highest concentration in soft tissue. After 100 days over 99% of the total body burden (about 0.4% of the administered dose), was found in bone, with a biological half-time of about 1100 days, the slowest of a three component elimination curve.

There is no evidence that tungsten is essential either to man or animals.

The metabolism of tungsten is related to that of molybdenum which it closely resembles in chemical properties. Sodium tungstate antagonizes molybdate in its role as metal carrier for xanthine oxidase. It is likely that tungsten can preferentially occupy enzyme sites normally occupied by molybdenum.

Little is known of the toxicity of tungsten compounds, although the LD_{50} of soluble salts in the rat is relatively high. Tungsten and its compounds are not an important human health hazard. Following occupational exposure to tungsten carbide dust by inhalation, cases of pulmonary fibrosis have been reported, but this "hard metal disease", as it is often called, is more likely to be caused by cobalt, with which tungsten carbide is fused.

2. Physical and chemical properties

Tungsten, W, atomic weight 183.9; atomic number 74; melting point 3410°C; boiling point 5900°C; specific gravity 19.3; valence 6,5,4,3 and 2; crystalline form gray-black, cubic.

Tungsten, known also as Wolfram, belongs to Group 6 of the periodic system, together with molybdenum and chromium. Tungsten is not oxidized in air at ordinary temperatures and is highly resistant to acids. Its chemical properties resemble those of molybdenum. Among the more common compounds are the canary yellow trioxide, tungstic acid, sodium tungstate, ammonium paratungstate and tungsten carbide.

3. Methods and problems of analysis

Aull and Kinard (1940) detailed a spectrophotometric method based on thiocyanate and stannous chloride for the estimation of tungsten in biological materials. However, nickel and cobalt may interfere with the estimation if present in comparable amounts. The detection limit could be improved to 0.7 mg/kg by a concentration procedure described by Wilson and Fields (1944). Estimation of trace concentrations of tungsten occurring in air and in water can be performed by instrumental neutron activation analysis using automatic gamma-ray spectroscopy with a high degree of accuracy (Salmon, 1974; Cawse, 1974). The detection limit of their method, using a thermal neutron flux up to 10^{14} n · cm^{-2} sec^{-1} for activation, was 2 ng/kg for industrial air and 10 µg/kg for industrial rainwater. These limits were based on 98% confidence levels and the precision of the method was estimated at 5-10%.

4. Production and uses

4.1 Production

Wolframite and Scheelite are the common, naturally occurring sources of tungsten, the richest deposits being found in China, Alaska and Mexico. The world production in 1973 was 48,230 metric tons. The ore in crushed and ground, concentrated by various physical processes, converted to the oxide and reduced to the metal. Tungsten carbide is produced by heating the finely powdered metal intimately mixed with carbon in an atmosphere of hydrogen in an electric furnace. In the production of tungsten carbide tools, the carbide is sintered with cobalt which acts as a binder. The sintered material is then ground to its final shape.

4.2 Uses

Tungsten is a valuable metal because of its high melting point, great strength at high temperatures and good conductivity for electricity and for heat. It is used to increase the hardness and tensile strength of steel; it plays a vital role in the production of a number of other alloys noted for their hardness, such as the chromium, cobalt and tungsten alloy used for tipping and facing lathe tools. Many drills and cutting edges of tools are tipped with tungsten carbide which gives them a hardness comparable to that of diamond. The metal is used for making filaments for incandescent lamps, and tungstates are used in X-ray tubes, fluorescent lamps in lasers, and as pigments in dyes and inks. Tungsten has more recently acquired importance in nuclear and space technology in the nozzles of rocket motors and protecting shields for space craft.

5. Environmental levels and exposures

5.1 General environment - Food, water, soil and ambient air

The dietary intake of tungsten, estimated by neutron activation analysis in 4 subjects, ranged from 8.0 to 13.0 μg/24 hours over a total of 8 total diet estimations (Wester, 1974). Drinking water sampled in the 3 largest Swedish cities varied in tungsten concentration from 0.03 to 0.1 μg/l depending on the sampling site. Neutron activation analysis was used (Boström and Wester, 1967). In a survey of atmospheric trace elements in the United Kingdom performed during 1972-73, again by neutron activation analysis, tungsten was included in the "very low" category. Concentration in rainwater was found to be less than 1 μg/l in 5 out of 7 sampling stations. Total deposition of tungsten was found to be less than 2 μg cm^{-2} year^{-1} at all 7 sampling stations and less than 0.1 μg cm^{-2} year^{-1} at six of these. Only very small concentrations of tungsten have been found in the atmosphere, and these have been related to industrial emissions or to nuclear fallout. Levels have usually been less than 1 ng/kg air (Cawse, 1974).

5.2 Working environment

A large amount of dust can be released from the crushing and milling of the ores wolframite and scheelite. In the loading and emptying from furnaces of graphite boats containing the reduced metal, air concentrations of tungsten and of tungsten trioxide of 10 and 46 mg/m^3 were obtained (Mesentseva, 1963). In the various processes associated with tungsten carbide manufacture, air concentrations as high as 47 mg/m^3 were measured (Mesentseva, 1963). Dust may be produced during the mixing of the components and also in the shaping and grinding of the products. Coates and Watson (1971) described metal particles in the atmosphere with a mean diameter of 1.2 to 1.9 mu. In the tool cutting industry exposure occurs not only to the dust of tungsten carbide but also to cobalt fume and dust and to the carbides of nickel, titanium and tantalum.

6. Metabolism

Tungsten has not been shown to be an essential trace metal in either animal or plant metabolism. The tungstate ion, $WO_4^{=}$, is the most soluble and frequently occurring form of tungsten in biological systems.

6.1 Absorption

A detailed study on the absorption, distribution and retention of ^{187}W has been performed on the rat (Kaye, 1968). The radioisotopes in the form of tungstate in alkaline solution were administered by gastric intubation and followed, in the case of ^{185}W for periods up to 254 days. A large part of the ingested tungsten was absorbed. The rapid absorption of tungsten from the gut could be demonstrated by the peak value of 17% of the administered dose in the carcass 1 hour after administration. After 4 hours 9 % had remained in the carcass and 12% had been excreted in the urine, while after 24 hours only 3% had remained in the carcass and about 40% had been excreted in the urine. This activity was due to rapid uptake by plasma followed by clearance by renal filtration. During the first hour, all the radioactivity in whole blood was in the plasma, but this was followed by transfer of tungsten from plasma to cells and by incorporation at sites of hemopoiesis.

6.2 Distribution

Rats were fed for a period of 100 days on diets in which tungsten had been incorporated either as the finely ground metal, tungstic oxide, sodium tungstate or ammonium paratungstate (Kinard and Aull, 1945). The principal sites of deposition were bone and spleen with smaller quantities, of the order of less than 10 mg/kg of tungsten in kidney and liver. Concentrations of tungsten less than 10 mg/kg were reported as a trace; traces of tungsten were also found in blood, lung, muscle and testis. No marked difference in distribution of tungsten was found with the different compounds ingested.

Long term studies in rats of ^{185}W administered by stomach tube (Kaye, 1968) showed that after 100 days over 99% of the total body burden (about 0.4% of the administered dose) had been retained in bone. In soft tissues, the highest concentration was found in spleen, thought likely to be due to the sequestering action on red blood cells. The next highest concentration was in hair, but external contamination could not be excluded. The relatively high concentration of tungsten in the kidney on the third day correlated well with the large fraction of the administered dose eliminated in urine and the shape of the kidney retention curve reflected this.

6.3 Excretion

In the study detailed above (Kaye, 1968) about 40% of the administered dose of ^{187}W had been excreted by the kidney in the first 24 hours. Very little was excreted in the urine subsequently. The further 40% of the administered dose recovered from the feces by 24 hours is likely to have been accounted for by unabsorbed tungsten together with tungsten excreted into the gut with intestinal secretions and with bile. In man, trace quantities of tungsten are excreted in urine and feces (see section 7). In a limited study on 4 normal young adults, the excretion by these two routes over 24 hour periods balanced the tungsten intake in food, with only small positive and negative variations (Wester, 1974).

6.4 Biological half-time

In the study by Kaye (1968) elimination of tungsten from the whole rat was very rapid with a biological half-time of about ten hours for the initial fast component of the elimination curve. Elimination from soft tissues was relatively rapid with a biological half-time of 44 days for the spleen. The biological half-time for ^{185}W in bone was calculated at 1100 days for the slowest component of a three component elimination curve.

7. Normal levels in biological tissues and fluids

Information on this aspect is scanty. Kinard and Aull (1945) were unable to detect tungsten in any of the tissues of their control group of animals in their oral dosing experiments referred to in section 6.2.

In man, the mean serum concentration of tungsten, estimated by neutron activation analysis, was found to be 5.8 ng/ml in 8 healthy subjects, with a standard deviation of 3.5. In 11 patients with hypertension the mean serum level was 11 ± 13 ng/ml before treatment and 16 ± 18 ng/ml after treatment with chlorthalidone. None of these differences were significant (Wester, 1973).

The urinary excretion of tungsten, again measured by neutron activation, ranged from 2.0 to 13.0 µg/24 hours in four subjects over 8 estimations. Fecal excretion in the same subjects ranged from 1.6 to 5.7 µg W per 24 hours. The subjects were healthy, young male and female adults in whom tungsten output did not appear to be affected by calcium intake in the diet in this small series of observations (Wester, 1974). In a group of 16 hypertensive patients, the mean tungsten excretion in the urine was 32 ± 63 (SD) µg per 24 hours before treatment, and 36 ± 85 (SD) µg for 24 hours during treatment with chlorthalidone. The levels showed great variability between individuals and were not influenced by diuretic therapy.

8. Effects and dose-response relationships

8.1 Respiratory effects

8.1.1 Animals

Tungsten metal and its compounds do not appear to have any significant effect on the respiratory system of the rat. Upon intratracheal instillation of pure tungsten carbide and tungsten metal in rats, Miller et al. (1953) and Delahant (1955) produced no cellular reaction other than that due to an inert dust. However, an intense inflammatory reaction resulted if cobalt was an ingredient in the injected material. Mezentseva (1963) gave white rats a single intratracheal dose of 50 mg metallic tungsten, tungsten trioxide or tungsten carbide in 0.5 ml saline and sacrificed the animals after 4, 6 and 8 months. Histological changes were limited to the lungs and consisted of a proliferative reaction of the lymphoid and histiocytic elements, particularly at the sites of accumulation of the administered dust, with subsequent mild fibrosis. The walls of small vessels were thickened and their endothelium swollen.

8.1.2 Humans

A hazard exists in the tungsten carbide industry, which takes the form of "hard metal disease". The agent responsible for this disorder is believed to be cobalt, present as a constituent of the hard metal alloy, but this has not been proven. Studies in a number of factories manufacturing tungsten carbide based products have revealed the presence of respiratory symptoms associated with impaired respiratory function and radiographic abnormality in a small proportion of those exposed. Moschinski et al. (1959) investigated 331 hard metal workers and found evidence of pulmonary fibrosis in 59. The characteristic radiographic appearances were of increased lung markings in the lower lung fields with nodular opacities in the more advanced cases. Ahlmark et al. (1961) described four cases in men who had not been exposed for more than eight years. Bech et al. (1962) described the clinical and radiological findings in six cases of hard metal disease collected over a period of 15 years. Complaints included cough, expectoration, shortness of breath, and tightness in the chest. In two of six cases pulmonary function tests showed mild alveolar diffusion defects, and in one worker who died, diffused pulmonary interstitial fibrosis was found. There was evidence of pulmonary fibrosis in the chest radiographs. In addition, a radiological survey was performed in 255 workers exposed to hard metal dust. This showed only slight changes in several of the workers and yielded one of the six cases described above. Airborne dust concentrations at the time of the survey were of the order of 0.10 mg/m^3 for particles less than 5 μm projected diameter. Gravimetric samples taken in the sieving room showed 90% tungsten and 6% cobalt in the incombustible fraction. It was concluded that the cause of hard metal disease was the inhalation of dust from the working environment but that the responsible component was likely to be cobalt rather than tungsten. The absence of cobalt from the lungs of hard metal workers, which contained both tungsten and titanium, was attributed to the high solubility of cobalt in plasma.

Coates and Watson (1971) described 12 cases, including 8 deaths, of diffuse interstitial pulmonary fibrosis in workers processing tungsten carbide. The clinical picture was of nonproductive cough, exertional dyspnea and weight loss. Respiratory function tests showed a restrictive pattern with an abnormality of gas transfer. The radiological appearances were characterized by progressive, bilateral nodular and linear shadowing involving major portions of both lungs. Detailed histological examination of three cases (Coates and Watson, 1973) showed deposits of collagen and elastic tissue in the septal areas, and alteration of the alveolar lining cells (modified type 1 pneumocytes) with swelling and formation of microvilli. Unidentified hard, multifaceted crystals were present in the affected areas of the lung. These authors, too, attributed the condition to the inhalation of cobalt containing dust.

8.2 Systemic effects and dose-response relationships

8.2.1 Animals

In a series of feeding experiments, young rats were fed for a period of 70 days with different concentrations of sodium tungstate, tungstic oxide and ammonium paratungstate mixed in Purina dog chow (Kinard and Van de Erve, 1941). Sodium tungstate, equivalent to 2% W, tungstic oxide equivalent to 3.96% W and ammonium paratungstate equivalent to 5% W were markedly toxic, causing initial weight loss followed by the deaths of all animals in each group within 10 days. In diets having an equivalent of 0.5% W, sodium tungstate and tungstic oxide produced death in three quarters of the rats, while ammonium paratungstate produced no fatalities. The same authors (1943) in similarly designed feeding experiments administered 2%, 5% and 10% tungsten metal powder over 70 days and found no effect on weight gain in male rats, but a 15% reduction in females.

In an extensive life-term study, Schroeder and Mitchener (1975) added 5 mg/l as sodium tungstate to the drinking water of rats. At this dose level there was little detectable effect as measured by serum cholesterol, glucose, uric acid and incidence of tumor formations. However, a slight enhancement on growth was seen in rats of both sexes and a small but significant shortening of longevity in the tungsten dosed male rats.

Tungstic acid has been used to produce experimental epilepsy in laboratory animals (Kusske et al., 1974). 0.02 ml of tungstic acid gel applied to the surface of the cortex in a series of cats gave rise to abnormal EEG activity after a 20 to 30 minute interval, which increased to give rise to sustained ictal activity.

Following the intraperitoneal injection of tungsten oxide in rats, no cellular reaction has been observed (Frederick and Bradley, 1946).

8.2.2 Humans

There are no data available on occupational exposures to compounds of tungsten which incriminate these as toxic or as hazardous agents. Kruger (1912) observed no ill effects in patients given 25 to 80 g powdered tungsten metal by mouth as a substitute for barium in radiological examinations.

8.3 Interaction with molybdenum

Sodium tungstate antagonizes the normal metabolic action of molybdate in its role as metal carrier for xanthine dehydrogenase. Higgins et al. (1956) showed that sodium tungstate added to the diet inhibited the intestinal deposition of xanthine oxidase in the rat and reduced both xanthine dehydrogenase and molybdenum concentrations in the liver of the chicken. Owen and Proudfoot (1968) fed sodium tungstate to goats and cows and showed a reduction in xanthine oxidase secreted in milk, in some cases to an undetectable level. They postulated that tungstate can preferentially occupy enzyme sites normally occupied by molybdate.

Cohen et al. (1973) administered tungstate to rats maintained on a low molybdenum diet and demonstrated a loss of both xanthine oxidase and sulfite oxidase activities. The tungsten treated rats appeared healthy, but were more susceptible to bisulfite toxicity. Upon exposure to high levels of sulfur dioxide, the tungsten treated, sulfite oxidase deficient animals showed evidence of systemic sulfite toxicity and had much shorter survival times than the controls. Sulfite oxidase appears to be involved in the oxidative metabolism and thus detoxification of sulfur dioxide as well as of bisulfite.

Sulfite oxidase activity in rat liver is negligible at birth but increases rapidly between the fifth and eleventh days after birth. Activity is considerably impaired by administration of tungsten for 20 days before delivery (Cohen et al., 1974).

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URANIUM

Maths Berlin and B. Rudell

1. Abstract

Uranium occurs in the mammalian body in soluble form only as tetravalent uranium or hexavalent uranium as uranyl complexes. Both hexavalent and tetravalent uranium form complexes with carbonate ions and proteins in the body. Oxidation of tetravalent uranium to hexavalent uranium is likely to occur in the organism. Absorption of uranium salts may occur by inhalation or by ingestion. 95% of retained uranium in the body is deposited in bone. Excretion is mainly by the kidney. There is no evidence that uranium has any metabolic function in the mammalian organism. As all uranium isotopes in nature are radioactive, the hazards of a high intake of uranium are two-fold - chemical toxocity, and irradiation damage caused by the radioactive emission from the uranium isotope.

The critical organ for the chemical toxicity is the proximal tubule of the kidney. The chemical injury reveals itself by increased catalase excretion in urine and proteinuria in man. Such changes are likely to occur when uranium concentration in the kidney exceeds 1 mg/kg. The concentration of uranium in the kidney is mainly dependent on the solubility of the uranium compound to which the individual is exposed.

The daily intake of uranium is of the order of 1.5 μg/day, mainly derived from food items like vegetables, cereals and table salt. Occupational exposure involves exposure to dust particles containing uranium compounds with different solubility and of varying size and density. Uranium concentrations in air up to several 100 μg/m^3 have been reported for some occupational conditions. Insoluble uranium particles

may be retained in the lung for a long time and constitute a radiological hazard there.

The toxicology and radiological hazards of uranium compounds have been extensively investigated as part of the Manhattan project during the Second World War. This work has been summarized recently by Hodge et al. - "Uranium, Plutonium, Transplutonic Elements".

2. Physical and chemical properties

Uranium, U; atomic weight 238; atomic number 92; density ~18.95; melting point 1132.3 ± 0.8°C; boiling point 3818°C; crystalline form silvery, cubic, radioactive; oxidation state 3,4,5 or 6.

Uranium occurs in nature in three isotopic forms - U-238 (natural abundance 99.25%), U-235 (0.71%) and U-234 (0.0057%). U-238, half-time $4.5 \cdot 10^9$ years; α-energies ~4.2 MeV - 100%; γ-energies 0.048 MeV - 0%; U-235, half-time $7.1 \cdot 10^8$ years; α-energies 4.8 to 4.56 MeV; γ-energies 0.095 MeV - 9%, 0.143 MeV - 12%, 0.185 MeV - 55%; U-234, half-time $2.5 \cdot 10^5$ years; α-energies 4.717 MeV - 28%, 4.768 MeV - 72%; γ-energies 0.051 MeV - 0%. Pure uranium metal is very reactive as a strong reducing agent (Hodge et al., 1973).

Uranium occurs in physiological systems in soluble form only, in a tetravalent or hexavalent state as uranyl ions $(UO_2)^{+2}$. Both hexavalent and tetravalent uranium form complexes with carbonate ions and proteins in the body.

3. Methods and problems of analysis

In the determination of the uranium content of biological samples, the organic material must first be destroyed by ashing or by acid treatment. Interfering substances may be removed by ion-exchange or by solvent extraction after the addition of appropriate chelating agents. After uranium recovery has been ascertained through these separation techniques, the uranium content of the purified sample may then be determined by mass spectrometry (detection limit $2\cdot10^{-12}$g), fluorimetric method ($1\cdot10^{-8}$g) or radiometric methods ($1\cdot10^{-9} - 1\cdot10^{-12}$g).

In fluorimetric determination, sodium fluoride is activated with uranium upon which it becomes very brightly fluorescent (yellow-green, 5546 Å) when illuminated with ultraviolet radiation of 3650 Å (Australian Atomic Energy Commission, 1970). This fluorescence is specific for uranium (Analytical Chemistry of Uranium, 1963).

Many elements such as silver, gold, cerium, cobalt, chromium, copper, iron, manganese, nickel, lead and thorium produce marked quenching effects when present in microgram amounts (Australian Atomic Energy Commission, 1970). Therefore a preliminary separation of uranium must be carried out.

Radiometric methods are based on the spontaneous radiation emitted by uranium and its decay products or the radiation induced by nuclear reactions caused by particle irradiation. Depending on the uranium isotope composition of the sample, the uranium content can be determined by measuring alpha and/or gamma irradiation combined with pulse height analysis. It is necessary that a standard containing material of the same isotope composition as the sample be used.

In neutron activation analysis the uranium or a specific uranium isotope can be determined by a number of nuclear techniques including direct α-counting (Campbell, 1955; Kurtz, 1956; Frigerio, 1970), delayed neutron counting (Amiel, 1962; Kramer, 1967; Donoghue, 1972), fission track counting (Carpenter, 1970), and nuclear activation techniques utilizing Np-239 daughter of U-239 (Edington, 1967; Picer, 1968), several different fission products of U-235 (Smales, 1952; Busselli, 1965; Ikeda, 1969; Weaver, 1974), and a number of procedures using the nuclear reaction U-238 (n,γ)-U-239 (Sankar Das, 1962; Decat, 1963; Kramer, 1967; Nosaki et al., 1970).

4. Production and uses

4.1 Production

Uranium is produced in about 15 countries. 80% of the production outside the Soviet Union and China - about 30,000 tons of uranium per year - takes place in the United States (14,600 tons), Canada (4,600 tons) and South Africa (4,200 tons) (World Energy Conference, 1974). Production capacity in the Soviet Union and China is not known.

Open pit methods are often employed in mining uranium deposits, but underground mining is currently the principal method used in Canada, South Africa, and France, and for about half the production in the United States.

Uranium is soaked from the ore and separated from the leach solutions by ion exchange, solvent extraction or direct precipitation. Recovery commonly exceeds 90%. During the process, the uranyl ion (UO_2^{2+}) is converted into uranium hexafluoride (UF_6), a gas. The enrichment of $^{235}UF_6$ is achieved by membrane diffusion utilizing the mass difference between $^{235}UF_6$ and hexafluorides of other uranium isotopes. $^{235}UF_6$ is converted into uranium dioxide ($^{235}UO_2$), the final reactor fuel product. Uranium metal is prepared from uranium oxide and uranium halides by reduction.

4.2 Uses

The main use of uranium is as fuel in nuclear energy plants. To a smaller extent, uranium compounds have also been used as catalysts and staining pigments.

5. Environmental levels and exposures

5.1 General environment

5.1.1 Food and daily intake

Food products such as potatoes, bakery products, meat and fresh fish contain uranium concentrations between 10 and

100 μg/kg according to Prister (1969). Concentrations of magnitudes 2 orders lower have been reported by Welford and Baird (1967) and Hamilton (1972). Hamilton found that table salt contained 40 μg uranium/kg and contributed considerably to the uranium content of prepared food. All cited investigators agree that vegetables and cereals contribute most heavily to the daily intake of uranium.

Based on analysis of uranium concentration in food products, Prister (1969) calculated the daily intake of uranium in the Soviet Union at around 30 μg. Similar estimates for three urban areas in the United States gave a daily intake of 1.3-1.4 μg/day with virtually no difference among the three areas (Welford and Baird, 1967). An estimate for the United Kingdom by Hamilton (1972) resulted in an average uranium intake of about 1 μg/day. Daily intake of uranium in Japanese urban areas has been estimated at 1.5 μg/day by Nozaki et al. (1970). Yamoto et al. (1974) reported daily intakes up to 4.55 μg in areas near uranium mines in Japan.

5.1.2 Water, soil and ambient air

High levels of uranium have been reported in drinking water derived from sources near rock of high uranium content. Values between 200 μg and 7 μg uranium/liter have been found (Novikov and Resanov, 1962; Berdnikova, 1964). A value of 32 ng uranium/liter has been reported in New York City tap water (Welford and Baird, 1967). According to Nozaki et al. (1970), drinking water in urban centers in Japan contains 4.8 to 11.4 ng/liter.

Uranium is a ubiquitous element, present in the earth's crust in an average concentration of about $4 \cdot 10^{-4}$ %; concentrations in sea water average around 3.3 μg/liter (Kenn, 1968). It is absorbed from the soil into plant tissues to an extent which is dependent upon the species of plant and the depth of its root system. Uranium occurs in higher concentrations in some minerals. Sources containing as little as 0.1 and up to 60% uranium are exploited commercially. Most ore deposits hold about 1% uranium or more.

Measurable concentrations of uranium in ambient air have been reported from the USA and the United Kingdom. Average concentration in the New York area was found to be 0.4 ng/m^3 (Welford and Baird, 1967). Corresponding values from the United Kingdom of 0.02 ng/m^3 have been reported by Dean (1967) and Hamilton (1970). Hamilton (1970) has further reported a uranium concentration of $3-4 \cdot 10^{-9}$ ng/m^3 in air over the Atlantic Ocean.

5.2 Working environment

Occupational exposure to uranium usually involves mixtures of different uranium compounds with solubilities in water at room temperature ranging from 1-400,000 mg uranium/liter. Dust particles containing uranium may be of varying sizes and densities. Density ranges from 2.8 to 10.9 g/cm^3 (Hursh and Spoor, 1973). Changes in particle size distribution and compound mixtures occur continuously in the work environment. Uranium concentrations in air of between a few μg/m^3 to several hundred μg/m^3 have been reported from different work environments.

6. Metabolism

Hexavalent uranium can be reduced intracellularly to tetravalent uranium. Oxidation of tetravalent uranium to hexavalent uranium is likely to occur in the organism. On entering the body, soluble uranium immediately forms complexes with anions, bases such as bicarbonate, citrate, malate, lactate, etc. (Dounce, 1949; Dounce et al., 1949; Gindler, 1973).

The uranyl compounds have great affinity for phosphate-containing molecules and tissues (Rothstein, 1951; Rich, 1975), carboxyl and/or hydroxyl groups such as proteins, nucleotides and bone tissue.

Absorption, retention and excretion of uranium are dependent upon its chemical form. The most crucial factor is the solubility of the compound in biological media. Other factors, such as particle size and surface characteristics, will affect the rate of phagocytosis and the transportability of relatively insoluble material in the body. According to Scott (1973), uranium compounds occurring in the environment can be classified as highly, moderately and slightly transportable. In Table 1 uranium compounds are listed under these headings. To the highly transportable uranium compounds belong the water soluble compounds. The moderately transportable compounds are less soluble but may also be transformed into hexavalent soluble compounds in the organism.

6.1 Absorption

6.1.1 Inhalation

There is little conclusive data in the literature about the rate of lung absorption upon inhalation of uranium compounds. Due to the high density of uranium-containing particles, most particles would have an aerodynamic size which will not permit them to be carried to the peripheral part of the lung. Based on measurements in some uranium plants (Harris, 1961), estimates have been made that only 1-5% of uranium-containing dust will penetrate to the pulmonary region. The rest will be deposited in the upper respiratory tract and will eventually be swallowed. The soluble compounds of uranium deposited in the alveolar region are likely to be absorbed to 100%. Less soluble particles can either be absorbed to a fraction or removed by the lung clearance mechanism. Measurements of lung burden of uranium in workers occupationally exposed to high levels of uranium in air support the conclusion that a low fraction of inhaled dust penetrates into the alveolar region (West and Scott, 1966, 1969; Schultz, 1968).

Animal data on deposition and absorption in the lung indicate large species differences (Spoor and Hursh, 1973).

6.1.2 Ingestion

Experimental data from both animals and man show that absorption in the intestinal tract varies with the solubility of the uranium compound. Even of the soluble compounds, only a small fraction is absorbed. In a clinical experiment on four patients, given 11 mg uranium in the form of uranium nitrate hexahydrate, 0.5-5% of the dose was found to be absorbed (Hursh et al., 1969). If data on daily intake as reported by Hamilton (1972) for the United Kingdom and Welford and Baird (1967) for three large American cities are combined with daily urinary excretion found by the same authors, absorption can be estimated at 12% in the American data and 31% in the British data. The dose in Hursh's study is about a thousand-fold higher than the average daily intake; these data thus suggest a dose dependence for absorption.

6.1.3 Skin

In animal experiments, water soluble uranium compounds have been shown to be absorbed by the skin in sufficient amounts to cause intoxication (Orcutt, 1949). Absorption can also occur from the conjunctival sac, as has been shown on experimental animals (Orcutt, 1949). Water insoluble compounds are not absorbed in detectable amounts. Human skin absorption data are not available.

6.2 Transport and biotransformation

Uranium tends to be converted in the mammalian organism into water soluble hexavalent uranium. Uranium forms soluble complexes with the bicarbonate ions and with proteins. Thus, uranium in blood is found complexed with the bicarbonate in plasma to 47%; 32% is bound to plasma proteins and 20% to erythrocytes (Chevari and Likhner, 1968). Tetravalent uranium introduced into the bloodstream either oxidizes into hexavalent uranium or forms colloidal uranium oxide in the plasma (Dounce et al., 1949).

6.3 Distribution

Uranyl compounds introduced into the bloodstream are rapidly distributed throughout the human organism. In experiments in humans only 6 minutes after intravenous administration, two-thirds of the injected dose left the bloodstream; after 20 hrs this figure had risen to 99% (Struxness et al., 1956; Luessenhop et al., 1958). In animals, the distribution process was found to be even more rapid (Neuman et al., 1948). The major part was rapidly excreted by the kidney, and the rest was deposited in the kidney and in bone. Under steady-state conditions, 85% of the body burden of uranium was found in bone provided that uranium deposited in the lung is excluded (Donoghue et al., 1972). More than 90% of the remaining uranium was in the kidney, and detectable amounts could be found in the liver. In case of inhalation of less soluble uranium compounds, uranium may be found in the bronchial lymph nodes as well as in the lung itself. In bone, uranium replaces calcium in the hydroxyapatite complex. In the kidney, most uranium is found in the proximal tubules. Walinder et al. (1967a, 1967b) have described a two-phase distribution with a high amount of uranium in the juxtamedular part of the renal cortex shortly after administration, and later a clearance of this zone and relatively higher concentrations in the most peripheral part of the renal cortex.

6.4 Excretion and retention

Hexavalent uranium is rapidly excreted by the kidney. The uranyl bicarbonate complex in blood is ultrafiltrable and filtrated by the glomeruli. Depending on pH of the tubular urine, some uranium will be reabsorbed in the tubules. At high pH, small amounts of uranium will be retained in the tubular walls. At low pH, the carbonate uranyl complex will be split and the uranyl ion will complex with the proteins on the walls, whereby the tubular function may be impaired. This mechanism has been verified in humans by experimental study (Bassett et al., 1948). More than 90% of hexavalent soluble uranium salt injected intravenously is excreted by the kidney and less than 1% by feces. The excretion pattern is characterized by a two-phase excretion, one very rapid phase during which 70% of the dose is excreted the first 24 hr, and a very slow phase with a half-time exceeding months. In a study on six patients given intravenous doses of between 6 and 70 μg/kg, Bassett et al. (1948) found that 50% of the dose was excreted in 3-10 hr, and 70-86% in 24 hr. The remaining 14-30% was excreted very slowly. Similar figures were found in another group of patients in a terminal state, given doses of between 172-900 μg/kg of uranyl salt. Struxness et al. (1956), Luessenhop et al. (1958) and Bernard et al. (1956) confirmed the described excretion pattern. The overall elimination rate of uranium under conditions of normal daily intake has been estimated to a half-time of between 180 and 360 days (Hursh and Spoor, 1973), assuming that the excretion of uranium by other routes than by urine is negligible and that the organism is in steady state under normal conditions. These estimates were based on the autopsy data collected by Hamilton (1970), who estimated the body burden of uranium to be around 100 μg, and the autopsy data of Welford and Baird (1967), who estimated the body burden to be around 80 μg. The authors also determined the daily urinary excretion and found it to be 0.38 (Hamilton, 1970) and 0.15 μg (Welford and Baird, 1967). Assuming a steady state, the fraction of the whole body burden excreted per day becomes $\frac{0.15}{80}$ and $\frac{0.38}{100}$, which corresponds to half-times of 180 and 360 days.

The elimination rate of insoluble uranium compounds deposited in the lung has been studied in both animal experiments and by measuring the gamma emission from uranium deposited in the human lung. The lung burden of uranium has been followed to determine the elimination curve. It has to be emphasized that the rate of deposition and clearance of uranium-containing particles will be dependent on the chemical form and particle size. In a five-year exposure study on dogs, monkeys and rats exposed to uranium oxide UO_2 dust, the overall biological half-time for uranium deposited in the lung was found to be around 15 months for monkeys and dogs (Leach et al., 1973). Reports from human subjects occupationally exposed to insoluble uranium compounds have been summarized by Hursh and Spoor (1973). From the available material, it appears to be a two-phase clearance rate with a short phase with a biological half-time of between 11 and 100 days, and a slow phase with a long retention time and a biological half-time of between 120 and 1,500 days.

7. Effects and dose-response relationships

There are two hazards connected with exposure to uranium compounds: the renal damage caused by the chemical toxicity of the soluble uranium compounds, and the injury caused by the radioactive irradiation from the disintegration of the uranium isotopes. Which of these two hazards will be the limiting factor for exposure to uranium compounds is dependent upon the solubility of the compound, its route of administration and its isotope composition. The isotope most dangerous from the point of view of radiation, Uranium 235, comprises less than 1% of natural uranium, but is enriched during the production of nuclear fuels. Higher fractions of Uranium 235 increase the irradiation risk.

As the retention time in the body is the important factor for the irradiation risk, exposure to insoluble particles which are deposited and retained in the lung for a long time, constitutes a radiological hazard. Under these circumstances, renal uranium load should be low. The chemical toxicity of uranium will be the limiting factor after exposure to soluble compounds, when large quantities of the element will pass through the kidney. The following discussion will be limited to the chemical hazard; for a detailed discussion of the radiological hazard, the reader is referred to Hursh and Spoor (1973).

In experimental animals, the renal injury caused by uranium manifests itself some days after exposure as a change in the proximal convoluted tubules. Cell necrosis appears in the lower portions of the convoluted tubules and may extend to other parts of those structures. Hyaline casts, or casts containing shedded necrotic cells, are present at all levels of the tubular system. If the dose is not lethal, regeneration of the injured epithelium begins after 2-3 days; regrowth is complete within 2-3 weeks, but this new epithelial lining differs morphologically from normal tubular epithelium. The morphological damage has been described through electron microscopy by Stone et al. (1961); the appearance of the regenerating epithelium and the structure of the regenerating cells has been electron microscopically depicted by Porte et al. (1963). In animal experiments, a tolerance to uranium has been observed after exposure to sublethal doses of uranium compounds. This tolerance has been connected with the regenerated tubular epithelium, which differs both morphologically and histochemically from normal epithelium. If uranium exposure is discontinued, the regenerated epithelium will gradually be transformed into normal tubular epithelium.

Parallel with the tubular damage, changes in the glomeruli appear, affecting largely the basement membranes of the glomerular capillaries, which have been shown electron microscopically to involve loss of foot processes and dense deposits between the basement membrane and the epithelium, as well as hyaline droplets, other cytoplasmic bodies, myaline figures and cytoplasmic vacuoles in epithelial cells (Stone et al., 1961). The corresponding functional changes in the kidney are characterised by proteinuria, impaired diodrast and PAH clearance, and increased clearance of animoacids and glucose. Inulin and creatinine often remain virtually normal, though after severe damage they may decrease. All changes reflect damage to the lower two-thirds of the proximal convoluted segment of the proximal tubules.

In animal and human experiments, the earliest observed sign of renal tubular damage caused by uranium has been an increase in urinary catalase and albuminuria (Dounce et al., 1949; Luessenhop et al., 1958). The determination of urinary catalase is therefore a good control test for kidney function in uranium exposure. Such tests should preferably be combined with one for proteinuria.

Neurological signs and pathological changes in the cerebral and cerebellar cortices have been observed in rabbits exposed to soluble uranium salts. Verne (1931) and Purjess et al. (1930) noted epithelial degeneration of the choroid plexi in the brains of dogs exposed to toxic doses of soluble uranium salts.

Five years of exposure to uranium oxide (UO_2) has produced lung tumors in dogs (Leach et al., 1971), probably due to radiation injury. There is evidence only of renal injury in humans exposed to uranium compounds.

8. Dose-response relationships for the renal effects

Dose-response data for the toxic effect of uranium on the human kidney are scarce. The dose can be defined as uranium concentration in the kidney or as absorbed uranium in the body or as degree of exposure to uranium compounds. Conclusive data are available only for concentrations of uranium in the kidney and amount of uranium absorbed. In animal experiments, between 1 and 3 mg/kg kidney tissue produces mild renal damage in more than 10% of the animals (Voegtlin and Hodge, 1953). In experiments with single intravenous injections of uranium nitrate to volunteers or terminally ill patients, between 70-100 µg/kg body weight produced proteinuria and increased catalase excretion (Bassett et al., 1948; Luessenhop et al., 1958).

9. Indices of exposure and concentration in critical organ

As uranium excretion, distribution and absorption are dependent upon the type of exposure and the chemical composition of the compound as well as its solubility, there is no generally applicable index of exposure or body burden of uranium. However, urinary excretion of uranium has proved of practical value under conditions of exposure to appreciable amounts of soluble uranium salts. Thus, urinary excretion of uranium may reflect recent exposure levels and can be used for routine checking of exposure conditions. The establishment of acceptable levels must be made, in each case, with consideration to the type of exposure. Although it is not unlikely that urinary excretion of uranium may reflect the concentration of uranium in the critical organ for chemical toxicity - the kidney there are as yet no available data confirming this. In cases of uranium salt retention in the lungs after exposure to insoluble compounds, the critical organ is the lung, and the critical effect the radiation injury to the lung. In vivo measurements of pulmonary uranium burden by whole body scintillation counting are commonly used for routine control.

10. Prognosis and treatment of chemical injury to the kidney caused by uranium compounds

Experimental evidence suggests that if death from acute renal failure can be prevented, the prognosis for regression and regeneration of the renal tubular damage is good. Cases of uranium poisoning should be treated by intravenous infusion of sodium bicarbonate. The bicarbonate ion will complex-bind uranium in the blood, facilitate excretion and prevent resorption of uranium in the renal tubules (Newman et al., 1949). Experimental and clinical data indicate that a certain tolerance to uranium may develop during prolonged exposure (MacNider, 1929; Yuile, 1973).

Table 1. Classification of uranium compounds according to transportability (From Scott, 1973).

Highly transportable	Moderately transportable	Slightly transportable
UF_6	UO_2a)	UO_2a)
UO_3a)	U_3O_8a)	U_3O_8a)
$UO_2(NO_3)_2$	UO_3a)	uranium oxides
UF_4a)	UF_4a)	uranium hydrides
uranium sulfates	uranium nitrates	uranium carbides
uranium carbonates		salvage ash

a) Subjecting a particular uranium compound to higher temperatures tends to decrease rate of transportability.

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ZINC

Carl-Gustaf Elinder and Magnus Piscator

1. Abstract

Absorption of ingested zinc is highly variable, from 10 to 90% and is affected by various factors. High zinc concentrations are found in prostate, bone, muscle and liver. Excretion takes place mainly via the gastrointestinal tract. The biological half-time of retained ^{65}zinc in humans is in the order of half a year. Homeostatic mechanisms exist for gastrointestinal absorption and excretion of zinc.

Zinc is an essential metal, necessary for the function of several enzymes. Zinc deficiency is easily produced in animals and has been recorded in humans.

Large oral doses of zinc salts cause gastrointestinal disorders including vomiting and diarrhea. The emetic dose of zinc as a salt is about 300 mg. Metal fume fever is an acute disorder seen after respiratory exposure to freshly generated zinc fumes (mostly as ZnO). The syndrome has not been seen in working atmospheres with zinc concentrations below 15 mg/m^3.

Exposure to high concentrations of $ZnCl_2$ may be fatal, involving acute damage to the mucous membranes of the nasopharynx and respiratory tract. Chronic zinc poisoning among humans has not been described.

Reviews on zinc have been made by Athanassiadis (1969) and Halsted et al. (1974).

2. Physical and chemical properties

Zinc, Zn, atomic weight 65.4; atomic number 30; density 7.1; melting point 420°C; boiling point 907°C; crystalline form bluish-white metal, hexagonal; oxidation state 2.

Zinc is a relatively soft metal and has a strong tendency to react with inorganic compounds (as oxides, sulfates, phosphates) as well as organic ones. The compound most commonly used in industry is zinc oxide, which has a low solubility in most solvents. Other compounds to be taken up in this chapter are zinc sulfate, zinc carbamate, zinc chloride and zinc ammonium sulfate.

3. Methods and problems of analysis

Previously, the most common method for zinc analysis was the dithizone method. Zinc forms a colored complex with dithizone, which is extracted into an organic solvent and measured colorimetrically. The detection limit is around 0.7 mg/l in water solution (Hibbard, 1937; Sandell, 1959).

Atomic absorption spectrophotometry is at present the most widely used method for the analysis of zinc, for which it is well suited as well as having a large capacity. The detection limit in water is 0.5 to 1 µg Zn/l. The limit of detection of AAS is sufficient to permit measurements of zinc in air and in most biological materials such as tissues, blood, serum and urine (Sunderman, 1973). Other analytical methods in use are emission spectrography and neutron activation. Due to the good agreement among zinc concentrations in various materials, reported by different authors in different countries, the accuracy of the zinc analysis employed may be considered as sufficient (Halsted et al., 1974).

4. Production and uses

4.1 Production

The world production of zinc is at present steadily increasing at a rate of about 5% per year, from about 0.5 million metric tons in 1900 to about 5.5 million tons in 1972 (Teworte, 1973).

The principal ores of zinc are sulfides such as sphalerite and wurtzite (cubic and hexagonal ZnS). Zinc ore is mined to a great extent in USA, USSR and Japan. During blasting and crushing of the ore moderate losses of zinc to the atmosphere occur. Treatment of the crush by means of wet flotation may result in emissions into water. During smelting there are often large emissions of zinc into the air, which often also will result in cadmium emissions. The total emission of zinc into the atmosphere during smelting activities in the USA during 1969 has been estimated at about 50,000 tons (Davis, 1972). Significant zinc contamination of soil is only seen in the vicinity of point sources (Buchauer, 1973).

Zinc obtained by "recycling" accounts for 16% of the US yearly production (Fulkerson et al., 1973).

4.2 Uses

Zinc has been used by mankind for more than 2,000 years. The Romans mixed a zinc ore with copper to yield brass (Dawkins, 1949). At the end of the 18th century zinc began to be produced on a commercial scale.

Major uses of zinc are in the production of non-corrosive alloys, brass and in galvanizing steel and iron production. Zinc undergoes corrosion on the surface and protects the enclosed metal from degradation. Such products appear widely in e.g. automobile parts and household appliances.

Zinc oxide used in rubber and as a white pigment accounts for the largest quantities of zinc. Zinc sulfate is employed in human medicine in treating zinc deficiency. The carbamate has been utilized as a pesticide. Even zinc compounds of high purity may contain significant amounts of more toxic metals, e.g. cadmium and lead (Smit and Backe-Hansen, 1973).

5. Environmental levels and exposures

5.1 General environment

5.1.1 Food and daily intake

Halsted et al. (1974) summarized studies on the average daily intake of zinc in different areas and arrived at a figure on the order of 5 to 22 mg/day. In general, protein-rich foods, such as meat and marine organisms, oysters in particular, have high concentrations of zinc (10–50 mg/kg wet weight), whereas grains, vegetables and fruits are low in zinc, usually less than 5 mg/kg. Human milk contains about 3 mg/l (Schlettwein-Gsell and Mommsen-Straub, 1970).

The refining and preparation of food may result in a decrease of the zinc content (Schroeder, 1971).

5.1.2 Water, soil and ambient air

In sea and fresh water the concentration of zinc is around 10 µg/l (Durum et al., 1971; Preston et al., 1972). Drinking water generally has the same concentration as fresh water. Considerably higher zinc content (up to 2,000 µg/l) has, however, been recorded as a result of the passage of water through zinc-containing pipes (Schroeder et al., 1967).

The average concentration in the earth's crust is estimated at 40 mg/kg. In soil the zinc concentration varies between 10 and 300 mg/kg dry weight (Swaine, 1955; Wedepohl, 1972). Contamination by zinc smelters may increase these values considerably. Burkett et al. (1972) found about 50 times higher zinc concentrations (5,000 mg/kg) in soil close to a smelter compared with a control area.

In 58 air samples from cities in the USA zinc concentrations ranged from less than 0.01 to 0.84 µg/m^3; in 29 samples from nonurban areas the corresponding figures were 0.01 to 0.2 µg/m^3 (Schroeder, 1970/ original data from National Air Sampling Network, 1968, and Tabor and Warren, 1958/).

5.1.3 Plants

The normal levels of zinc range from 10 to 100 mg/kg in most crops and pasture plants. Zinc was early established as essential for the growth of higher plants (Brenchley, 1914). Insufficient concentration of zinc is a common micro-nutrition deficiency in crops (Lindsay, 1972) and zinc addition to soil with fertilizers is common. Toxicity of zinc among plants is rarely seen in areas other than those close to some emission sources.

5.2 Working environment

Exposure to zinc fumes, particularly ZnO, is a potential risk wherever zinc oxide is a product or by-product, e.g. in zinc smelting, manufacture of zinc oxide and powder, production of brass, and melting of galvanized iron. These processes yield a dispersion of zinc oxide particles of about 1 u Ø in the atmosphere (Athanassiadis, 1969). In a Polish shipyard, working zone averages of ZnO ranged from 1.5 to 18.0 mg/m^3 (Chmielewski et al., 1974).

6. Biological function and metabolism

6.1 Biological function

Zinc has been shown to be necessary for the function of various mammalian enzymes. At least 18 zinc metallo-enzymes have been identified (Parisi and Vallee, 1969), e.g. carbonic anhydrase, alcohol dehydrogenase and leucine-aminopeptidase. The two former are necessary for cellular oxidation while leucine-aminopeptidase is considered to be engaged in protein reabsorption in the proximal tubule of the kidney (Wachsmut and Torhorst, 1974).

Zinc deficiency decreases the production of DNA and RNA, which leads to reduced protein synthesis (see e.g. Holt et al. 1970; Prasad et al., 1974). The role of zinc in carbohydrate metabolism is still debatable, but one study indicates that zinc is necessary for a normal glucose balance (Macapinlac et al., 1966; Mills et al., 1969).

6.2 Zinc deficiency

6.2.1 Animals

Zinc deficiency has been described in most ruminants and laboratory animals. Deficient diets have usually contained less than 1 mg Zn/kg. Williams and Mills (1970), however, showed that growth arrest occurred among rats fed with food containing slightly less than 12 mg/kg of zinc. Typical signs of deficiency include dermatitis, emaciation, testicular atrophy, retarded growth, and anorexia. The simultaneous administration of cadmium enhances some of the effects of zinc deficiency. For example, Petering et al. (1971) observed a decreased growth rate and corneal keratinization among rats fed with a marginal level of zinc, when 3.4 mg/kg of cadmium was added in drinking water. The authors also observed that the zinc content of the testes then decreased.

6.2.2 Humans

Zinc is essential for human beings. The daily requirement for zinc has been recommended as 15 mg for adults and 25 mg for nursing mothers (Food and Nutrition Board, 1974).

An endemic zinc deficiency syndrome among young men has been reported from Iran and Egypt (Prasad et al., 1961; Halsted et al., 1972). Prominent features were retarded growth, infantile testis, delayed sexual maturation, anemia, hepatosplenomegaly and hyperpigmentation. Oral supplementation with zinc (30 mg/day) had a prompt, beneficial effect.

Acrodermatitis enterohepatica is a familial disease characterized by skin eruptions, gastrointestinal disorders and low serum zinc. One causative factor may be a low intestinal absorption of zinc. Complete cure is achieved by peroral administration of 135 mg zinc per day given as zinc sulfate (600 mg/day) (Michaelson, 1974).

There is some contention with regard to zinc and wound healing. Most workers have found a correlation between low serum zinc and poor wound healing, and several studies indicate a faster healing of venous and ischemic leg ulcers after oral zinc treatment (Hallböök and Lanner, 1972; Haeger and Lanner, 1974).

6.3 Metabolism

6.3.1 Absorption

No data are available which allow a calculation of pulmonary absorption.

The absorption of ingested zinc is also hard to ascertain since part of the absorbed zinc is excreted into the gut. As is the case for iron, some regulation of intake and output of zinc probably takes place in the intestinal membrane.

In animals, zinc absorption is highly variable and affected by various factors. Low body weight and poor zinc status increase absorption, whereas high oral doses of zinc and interfering substances in food such as calcium and phytate reduce it (Becker and Hoekstra, 1971). Zinc absorption has been reported to range from less than 10% to over 90%.

In humans, subjected to low doses of $^{65}ZnCl_2$ and whole-body measurements, Lombeck et al. (1975) estimated absorption to range from 58% to 77% in five controls and from 16% to 43% in three patients suffering from acrodermatitis enterohepatica. The whole-body zinc retention was measured for 34 days.

Absorption, by seven volunteers, of radio-zinc occurring as a contaminant in fishmeat was found to be around 35% by Honstead and Brady (1967).

6.3.2. Distribution

One week after an oral tracer dose of 2 μg $ZnCl_2$ to mice the highest concentrations were found in bone tissue followed by liver and kidney (Ansari et al., 1975).

6.3.3. Excretion

In animals given peroral or parenteral doses, ^{65}Zn is mainly eliminated via feces. In mice given 0.3 μg $ZnCl_2$ intravenously about 50% of the total dose was recovered in feces within a week. The corresponding figure in one week for dogs given 6.5 μg $ZnCl_2$ was about 20%. Urinary excretion during the same time was well below 5% of the dose in both species (Sheline et al., 1943). Biliary excretion of zinc in rats was found to be 4% during 48 hours following a single intravenous dose of 0.1 mg $^{65}ZnCl_2$ (Barrowman et al., 1973). Elimination of a single peroral dose of 2 mg ^{65}Zn increased sharply in rats pretreated with additions of unlabelled zinc to food, 600 mg/kg, compared to non-pretreated rats, indicating some homeostatic control for zinc (Ansari et al., 1975).

The daily elimination of ^{65}Zn in normal humans is on the order of 1% per day of absorbed perorally given radioactive zinc

(Sullivan and Heaney, 1970; Lombeck et al., 1975). About three quarters of the excretion take place via the gastrointestinal tract, and the rest via urine.

Concentrations of 0.6 to 0.7 mg/l have been found in the urine of workers exposed to zinc oxide in concentrations between 3 and 5 mg/m^3 (Mass. Div. of Occupational Hygiene, 1970, cited by ACGIH, 1971). These values are not excessively elevated compared to normal values (see section 7).

6.3.4 Biological half-time

As stated earlier, elimination of ^{65}Zn is related to zinc status, in such a way that additions of zinc in the diet increase the rate of elimination (see section 6.3.3).

In normal humans, without excessive intake of zinc, the body burden half-time of absorbed radio-zinc has been estimated at 162 days (Honstead and Brady, 1967). After parenteral administration of ^{65}Zn, half-times ranging from 250 to 500 days have been reported (Hawkins and Marks, 1976).

7. Normal levels in tissues and biological fluids

The highest concentration of zinc is found in the prostate, about 100 mg/kg wet weight. High levels of zinc are also found in bone, muscle, liver, kidney and pancreas. For more detailed results reference is made to the comprehensive review by Halsted et al. (1974). Levels of zinc in serum and plasma are constant, around 1 mg/l. The concentration of zinc in whole blood is about five times higher due to a ten times higher zinc content in red blood cells (Sunderman, 1973). Normal humans not occupationally exposed to zinc excrete an average of 0.5 mg/day in urine (Halsted et al., 1974).

8. Effects and dose-response relationships

8.1 Local effects and dose-response relationships

8.1.1 Animals

Rabbits, rats and cats exposed for 3.5 hours to zinc oxide fumes at concentrations of 110 to 600 mg/m^3 reacted with a transient fall in body temperature followed by a marked leukocytosis. In heavily exposed animals autopsy studies showed signs of bronchopneumonia (Drinker and Drinker, 1928).

Short-term exposure to zinc sulfate and zinc ammonium sulfate at about 1 to 2 mg/m^3 produced increased pulmonary air flow resistance in cats and guinea pigs. However, the sulfate had the main responsibility for this effect (Kincaid et al., 1953, Amdur et al., 1963).

8.1.2 Humans

8.1.2.1 Inhalation

Metal fume fever has been associated with inhalation of zinc oxide fumes, but other metals have probably been coexisting causative factors. Symptoms usually occur within a few hours after exposure, and have a short duration (6-48 hours). The typical manifestations are influenza-like with headache, fever, hyperpnea, leukocytosis, sweating, and pains in leg and chest. The illness is never fatal and affected subjects usually recover completely within two days (Rohrs, 1957; Stokinger, 1963; Browne, 1966; Hunter, 1969). The pathogenesis of the syndrome is not clear, but several indications of an allergic background have come forth. It has been proposed that zinc enters the blood circulation and forms a sensitizing complex with plasma proteins (Jaremin, 1973).

Data on air concentration of zinc oxide and exposure time causing metal fume fever are insufficient. Sturgis et al. (1927) exposed two volunteers to air concentrations of 600 mg Zn/m^3 (as ZnO). Moderate symptoms with typical febrile reaction and leukocytosis were recorded after 10.5 and 12 minutes' exposure.

Based on an occupational study conducted by Batchelor et al. (1926) (see section 8.2.2) it has been estimated that metal fume fever will not occur at air concentrations below 15 mg/m^3 (Hegsted et al., 1945).

Zinc chloride exposure may result in severe respiratory tract effects, with pneumonitis and fatal pulmonary edema. Dose-response relationships have not been reported.

It may be speculated that the high toxicity of $ZnCl_2$ is due to the formation of hydrochloric acid. Hunter (1969) reported on 70 workers exposed to an accidental release of $ZnCl_2$ from smoke generators. Ten workers died immediately or within a few hours and 25 workers experienced severe respiratory inflammation. Two necropsies showed membranes lining the larynx and trachea and edematous bronchi. One case of pulmonary fibrosis, which developed within 18 days after accidental exposure to $ZnCl_2$, has been described by Milliken et al. (1963).

8.1.2.2 Ingestion

Reports of toxic effects following ingestion of zinc are uncommon, and compared with most other trace metals zinc is fairly nontoxic.

Food poisoning attributable to galvanized zinc containers in food preparation has been reported (Brown et al., 1964). Symptoms occurred within 24 hours and included nausea, vomiting, diarrhea, in several cases with blood, and abdominal cramps. The emetic dose of zinc was estimated at 225-450 mg, corresponding to 1-2 g for the sulfate form.

Murphy (1970) described headache and lethargy in a boy who consumed 12 g of elemental zinc. Blood analysis showed elevated serum amylase, which indicated some effects on the pancreas.

8.2 Systemic effects and dose-response relationships

8.2.1 Animals

Excessive zinc addition to the food of weanling pigs (around 1,000 mg/kg for periods exceeding one month) produced depressed rate of growth and food intake. In addition, arthritis, lameness and inflammation of the gastrointestinal tract were recorded among the pigs (Grimmet et al., 1937; Brink et al., 1959). Similar signs of chronic toxicity from high dietary zinc intake have been found in horses (Willoughby et al., 1972).

8.2.2 Humans

Highly elevated serum zinc has been reported among some patients treated for renal failure by dialysis. This was brought about by a direct release of zinc ions from the equipment used into the blood (Blomfield et al., 1969). No ill-effect related to zinc was recorded.

Chronic zinc poisoning has not been described in humans. Patients suffering from venous leg ulcers have been treated for periods up to half a year with zinc doses on the order of 135 mg/day as the sulfate without toxic manifestations. Twenty-four workers occupationally exposed to 3 to 15 mg/m^3 for periods of two to thirty-five years did not show any signs of chronic toxicity (Batchelor et al., 1926).

However, it must be remembered that the highly toxic metal cadmium is closely related to zinc and will be obtained as a by-product wherever zinc is refined (Fulkerson et al., 1973). The possibility of cadmium exposure should always be taken into account when zinc and zinc compounds are handled. (See the chapter on cadmium in this series).

8.3 Carcinogenic and teratogenic effects

Repeated intratesticular injections of zinc chloride into chickens and rats have been reported to produce testicular sarcomas. There is no evidence that zinc compounds are carcinogenic after administration by any other route (Sunderman, 1976). Recently it has been reported that additions of 150 mg Zn/kg as zinc sulfate to the rat diet may be associated with harmful effects on the fetus (Kumar, 1976).

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